GEOGRAPHIC VARIATION IN THE INCIDENCE OF LEGIONNAIRES' DISEASE IN SCOTLAND.

RAJINDER SINGH BHOPAL

BSc. MBChB MRCP(UK) MPH MFCM

M.D.

UNIVERSITY OF EDINBURGH

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DEDICATION

I dedicate this thesis to my father who likes to ask questions, and to my mother whose devotion to work and family has been a fine example,

and

to my wife and children for supporting my endeavours to follow the footsteps of my parents.

DECLARATION OF RESPONSIBILITY, COLLABORATION, ORIGINALITY AND PUBLICATION

I declare that this report, and the research upon which it is based, is my work. I am responsible for the veracity of its content.

I have drawn upon the goodwill and expertise of others and have declared this in the acknowledgements. I wish to emphasise that the statistical analysis of the relationship between location of cooling towers and place of residence of cases was a collaborative effort; I provided the general understanding of the problem and colleagues at the Information Services Division (Edinburgh) the statistical and computing ability to produce the analysis in tables 7.6 and 7.7.

Table 2.6 is similar to table 7.4 in the book "Legionella Infections" by C L R Bartlett and colleagues. However, the structure and some of the contents of table 2.6 were prepared prior to the publication of the above book and included in my MFCM Part II examination report (Submitted September, 1986) on the Glasgow Legionnaires' Disease Outbreak.

This work has not been submitted for examination elsewhere but occasionally I have drawn upon my writings in the above-noted MFCM Part II Report.

A brief report concerning the material in appendix 3 has been published (Bhopal, 1989). A manuscript entitled "Maintenance of cooling towers in a city following two outbreaks of Legionnaires' Disease" has been accepted for publication (Epidemiology and Infection, in press).

Signature **Date** 1/11/1989

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The following individuals made substantial contributions to this project and I wish to record their help:

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LIST OF ABBREVIATIONS*

A&A	Ayrshire and Arran Health Board
A&C	Argyll and Clyde Health Board
Apr	April
Aug	August
B	Borders Health Board
BCYE	Buffered charcoal yeast extract
CDC	Centres for Disease Control
CFT	Complement fixation test
D & G	Dumfries and Galloway
Dec	December
DFA	Direct fluorescence test
DHSS	Department of Health and Social Security
ELISA	Enzyme-linked immunosorbent asay.
F	Fife Health Board
Feb	February
FV	Forth Valley Health Board
G	Grampian Health Board
GG	Greater Glasgow Health Board
GGHB	Greater Glasgow Health Board
H	Highland Health Board
IFAT	Indirect immunofluorescence test
Jan	January
L	Lanarkshire Health Board
Labs	Laboratories
LD	Legionnaires' Disease
LHB	Lothian Health Board
Lo	Lothian Health Board

No	Number
Nov	November
NS	not stated
O	Orkney Health Board
Oct	October
PHLS	Public Health Laboratory Service
RMAT	Rapid microagglutination test
RR	Relative risk
S	Shetland Health Board
SCO	Scotland
Sept	September
SHHD	Scottish Home and Health Department
SPSS	Statistical Package for the Social
T	Tayside Health Board
UK	United Kingdom
USA	United States of America
WI	Western Isles Health Board

* Abbreviations are mainly used in figures and tables.

DEFINITION OF TERMS AND CONVENTIONS

Community-acquired case	A patient with no apparent history of exposure to hospital during the 10 days prior to the illness i.e. not nosocomial.
Cooling towers	Wet type cooling systems including evaporative condensers.
Domestic water systems	Systems supplying water for non-industrial purposes, irrespective of the place supplied.
Immunofluorescence	In common with many reports this has been used rather than immunofluorescent (see IFAT, p xii).
Non-outbreak case	A case not recognised, at the time when this study started, as part of a cluster or outbreak.
Non-travel case	A patient who was not known to have travelled outside Scotland within 10 days of becoming ill
Nosocomial case	A patient with a history of visiting a hospital in the 10 days prior to illness, irrespective of

	whether there was proof that the source of infection was the hospital.
Outbreak case	One of two or more cases of Legionnaires' Disease associated in time and recognised to share a common source of infection.
Serological titres	The titre (endpoint dilution) is given e.g. 256 not 1/256.
Sporadic case	An isolated case, not associated with an outbreak. The term is often used to mean the same as non-outbreak as above in the literature but is generally avoided in this report for this reason: in the literature the meaning of the term has not been clarified, and details of which measures were taken to ensure that such cases were isolated are not provided.
Travel-associated	A patient who became ill within 10 days of returning from a journey outside Scotland
Travel-related	Synonymous with travel-associated.

THESIS*

From 1978 to 1986 the incidence of non-travel, non-outbreak Legionnaires' Disease in Scotland varied geographically and over time. The variations were not simply a result of errors in the case-list, changes or differences in the approach to diagnosis, or population differences in host susceptibility. Within the City of Glasgow the location of residence of cases and location of cooling towers were associated. The best explanation for the observations, and particularly those in Glasgow, is that cooling towers were a major source of both outbreak and non-outbreak infection.

* " a proposition laid down or stated, especially as a theme to be discussed and proved or to be maintained against attack".

(The Shorter Oxford English Dictionary, 1983)

UNIVERSITY OF EDINBURGH

ABSTRACT OF THESIS (Regulation 7.9)

Name of candidate R S Bhopal
Address Division of Community Medicine, Medical School, Framlington Place, Newcastle-Upon-Tyne NE24HH
Degree MD Date 31/8/89
Title of thesis Geographic Variation in the Incidence of Legionnaires'Disease in Scotland.
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The major sources of infection for Legionnaires' Disease, identified by study of outbreaks, are hot water systems and cooling towers. However, most cases are not part of outbreaks and, for these, the source of infection is rarely traced. The principle aim of this study was to help understand the source of non-outbreak infection by examining the epidemiology of the disease in Scotland.

Of the recognised cases which met the study case-definition, 366 were ill between 1978 to 1986 giving a mean annual incidence rate of 7.9 per million. The annual incidence varied in Scotland (range 3.1 to 20.2) and within health boards. Geographical variations were demonstrated by health board, by city and within cities, particularly for non-travel infection. For example, the cumulative incidence rate per million for non-travel, non-outbreak disease in Greater Glasgow Health Board (GGHB) was 130 compared to 45 for the whole of Scotland, and 11, 33 and 50 in Tayside, Lanarkshire and Lothian Health Boards respectively. Of 16 postcode sectors with a high incidence of disease in Scotland, 14 were in GGHB. In GGHB, the residence of non-travel, non-outbreak cases (but not of travel-related ones) was clustered in central areas. Previously unrecognised clustering was also found in other health boards.

These variations were not fully explained by differences in the population's exposure to diagnostic tests, as indicated by the number of serology tests requested by Scottish hospitals; the diagnostic service and approach of bacteriology laboratories; and the approach of hospital consultants to the diagnosis of Legionnaires' Disease.

Differences in host susceptibilty, as reflected by socio-economic status and the incidence of other respiratory disease, were small and did not explain the variation.

In the City of Glasgow, many cooling towers were not maintained in accord with recommendations and posed a theoretical risk of infection. The location of residence of non-travel cases was associated with the location of premises with cooling towers, the incidence of non-travel Legionnaires' Disease being more than three times higher in areas of Glasgow within 0.5 kilometres of a cooling tower than in areas more than one kilometre away.

The best explanation for these observations is that cooling towers were a major source of non-travel, non-outbreak infection. Hence, for the investigation and prevention of such infection, the emphasis should be on cooling tower maintenance. Close surveillance of apparently sporadic disease is recommended as the basis for disease control and future research.

CHAPTER 1

INTRODUCTION

Legionnaires' Disease is an environmentally acquired bacterial pneumonia caused by members of the genus Legionellaceae (Bartlett et al, 1986). These are aquatic organisms which are widely distributed in natural and man-made habitats (Fliermans, 1984). Transmission of the disease is by the airborne route and generally follows the inhalation, by susceptible people, of aerosols of water contaminated with pathogenic legionnellae. Person-to-person spread does not occur. Known sources of infective aerosols include evaporative cooling towers, showers, water taps, nebulisers and whirlpool spas (Bartlett et al, 1986). While the large, point-source outbreaks have been closely associated with evaporative cooling systems, in Britain, most clusters have been associated with exposure to aerosols from domestic water systems (Bartlett et al, 1986). However, as most cases of Legionnaires' Disease are sporadic, and these are seldom investigated in depth, the source of most infection remains unknown.

Legionnaires' Disease is an uncommon pneumonia yet it commands scientific and public attention. For the scientist there are two areas of interest: the chain of transmission which demonstrates so well the link between the natural and man-made environments and disease, and the potential for prevention. To the public the occurrence of Legionnaires' Disease in epidemic form is

frightening (Kass, 1977), and particularly disturbing when resulting from human failings e.g. the failure to follow water maintenance guidelines.

Potentially, Legionnaires' Disease could be prevented by the separation of man from the sources of virulent organisms, or by ensuring effective water hygiene. The rational implementation of preventive measures needs knowledge of the sources of infection and effective methods of suppressing the growth and dissemination of legionellae.

The core of this thesis is a study of the epidemiology of Legionnaires' Disease in Scotland to the end of 1986. Epidemiology is based on the description of disease in terms of person (who gets it), time (when did they get it) and place (where does the disease occur). If the disease varies by person, time, or place, hypotheses concerning the nature and causes of the disease may be developed. The focus of this study was on measuring the variation in the incidence of Legionnaires' Disease by place and on proposing and testing hypotheses to explain observed variation. The underlying aim was to seek further insight into the transmission of this disease, particularly of non-outbreak cases, in order to help develop prevention strategies.

Legionnaires' Disease is apparently commoner in Scotland than in most comparable countries, for example, the reported incidence is about three times that of England and Wales and the United States of America (Fallon and Abraham; 1982 Bhopal et al, 1988). The reason for the high incidence is unknown but one possibility is that Scotland has a centralised, accessible and experienced laboratory service and as a result diagnosis is more readily made. (This and other possibilities will be discussed later). Based on unvalidated, unpublished data (compiled by Dr. Martin Donaghey) from laboratory returns to the Communicable Diseases (Scotland) Unit, the incidence of Legionnaires' Disease in the period 1978 to June 1984 varied greatly from place to place within Scotland, and was highest in the Greater Glasgow Health Board. Greater Glasgow had 43% of the cases but only about 20% of the population of Scotland (incidence 16.5 per million) while Lothian had 21% of the cases and about 15% of the population (incidence = 10.5 per million).

Scotland has experienced two major outbreaks of Legionnaires' Disease, one community-acquired (Ad-hoc Committee,1986) and the other nosocomial (Timbury et al, 1986), and an outbreak of Pontiac Fever (Goldberg et al, 1988). In addition, a possible third outbreak has been reported (McEwan, 1986) but was regarded as sporadic by the health authorities.

Both the Scottish Legionnaires' Disease outbreaks were in the East End of the City of Glasgow. The geographical epidemiology of the community-acquired outbreak in Dennistoun (in 1984) had been important in guiding the investigation and in interpreting the findings (Ad-hoc Committee, 1986). Of 33 cases, 26 resided in Dennistoun (post-code G31) and the others worked or travelled there. An organism isolated from an evaporative condenser in an industrial site in the district was antigenically identical to that grown from two patients (Ad-hoc Committee, 1986; Tobin et al, 1987). When the cases were mapped by place of residence the pattern was fan shaped, with the industrial site being upwind at the stem of the fan. Two cases were housebound and lived 700 and 900 metres respectively from the postulated source of infection. These observations led to the hypothesis that aerosol from the evaporative condenser was carried by air currents and caused infection at a distance and possibly after entry to people's homes. The other outbreak, in Glasgow Royal Infirmary, was also associated with a cooling tower. All patients had been admitted to a high dependancy ward block which drew air from the roof of the hospital. Drift from the cooling tower was shown to enter the air intake and into the wards housing patients (Timbury et al, 1986).

Bhopal and Fallon (1988) examined the location of residence of the 1984 cases in the City of Glasgow and found that both outbreak and non-outbreak cases were commoner in the North of the City. The distribution of cooling towers, based on an unvalidated register of towers, was similar to the location of residence of cases suggesting that cooling towers may have been a major source of both outbreak and non-outbreak infection.

These events and observations led to several questions. Were the geographical variations by health board, as observed by Dr M Donaghey, artefact or real? Were the variations a result of differential clinical and laboratory practices or a consequence of variation in host susceptibility, agent virulence or environmental features? Had other Legionnaires' Disease cases occurred in the G31 area which were not recognised as part of the outbreak? Were there other clusters of cases which had not been recognised? Did the variation within Glasgow City observed for 1984 apply to other years? How accurate were the data on cooling towers? How well were cooling towers maintained? The quest for the answers to these and other questions led to the research journey outlined in Chapter 3.

Chapter 4, the backbone of the thesis, presents a retrospective review of the epidemiology of Legionnaires' Disease in Scotland to the end of 1986, with emphasis on

geographical variation. In Chapter 5 the question of whether the observed variations are artefacts of diagnosis or surveillance, or real is addressed. Chapter 6 considers the role of host susceptibility. The possible role of cooling towers in explaining the geographical pattern of disease in the City of Glasgow is detailed in Chapter 7. Also within this chapter is a summary of a survey attempting to locate cooling towers throughout Scotland, data on the quality of water in the City of Glasgow and observations on the maintainence of domestic water systems. Chapters 4, 5, 6 and 7 end in brief discussions of the methodology and of those results which are **not** central to the thesis. Chapter 8 concludes the main text of the thesis by discussing the principal results, making recommendations for surveillance and prevention of Legionnaires' Disease and suggesting directions for future research. First, the literature is reviewed.

CHAPTER 2

LITERATURE REVIEW

INTRODUCTION TO THE LITERATURE REVIEW

The principal aim of this review is to discuss the epidemiology of Legionnaires' Disease, and within this subject, to concentrate on the variation in incidence by time and place, and the mode of transmission of the disease (Part 2). To understand the epidemiology we need to consider the definition of the disease and its diagnosis and these topics are emphasised (part 1, sections c and e). The epidemiological review is preceded by less detailed accounts of the history of Legionnaires' Disease, the bacteriology and ecology of the organism, and the clinical features of the disease (part 1). Lastly, recommendations on the control of Legionnaires' Disease are presented (part 3).

PART I THE DISEASE AND ITS DIAGNOSIS

a) History: The Discovery of Legionnaires' Disease

One hundred and eighty two of the delegates to the 1976 American Legion Convention in Philadelphia became ill and 29 died from a pneumonic illness of unknown cause (Fraser et al, 1977). The name "Legionnaires' Disease" derives from this outbreak. An exhaustive search for the cause of the illness led to the discovery of a gram-negative bacterium to which patients had antibodies (McDade et al, 1977). The Legionnaires' Disease bacterium (later named *Legionella pneumophila*) was the

first of a newly discovered family of micro-organisms, the Legionellaceae.

Analysis of stored serum and bacterial cultures from some earlier outbreaks showed that these were also due to *Legonella* species (Thacker et al, 1978; Osterholm et al, 1983). The Tatlock Agent, isolated during the investigation of an outbreak of a febrile illness amongst soldiers in North Carolina in 1942 and 1943, was phenotypically identical to *L micdadei* (Hébert et al, 1980a, Hébert et al, 1980b). However, Fort Bragg Fever was not legionellosis; the Tatlock agent was probably adventitious (Winn, 1988a. The OLDA agent isolated from blood of a patient with bronchopneumonia in 1947 was identical to *L pneumophila* (McDade et al, 1979).

Outbreaks of respiratory illness in Austin, Minnesota, USA in 1957 (Osterholm et al, 1983), Washington, USA in 1965 (Thacker et al, 1978), Pontiac, USA in 1968 (Glick et al, 1978) and Benidorm, Spain in 1973 (Reid et al, 1978; Grist et al 1979) were, in hindsight, due to legionellae. The Benidorm outbreak led to the deaths of three Scottish men, the first known Scottish cases of the disease. The diagnosis of Legionnaires' Disease and the discovery of the Legionellaceae were new, but the disease was not.

Thereafter, development of knowledge was rapid. Epidemiological studies on outbreaks highlighted personal risk factors, and the role of cooling towers and potable water supplies as vectors of disease. By exclusion of other routes of transmission, the hypothesis that the organism was spread by the inhalation of aerosol was proposed (Fraser et al 1977). Animal studies as well as epidemiological observations supported the hypothesis. The Legionellaceae were found to be ubiquitous, aquatic organisms.

Since 1977 the reported incidence of disease has increased but this probably reflects increasing awareness of the disease and the wider availability of diagnostic tests. There is no firm evidence that Legionnaires' Disease is more common now than in the past (see section on epidemiology, secular trends) though the introduction of complex plumbing system which provide the warm water in which the organism thrives and the means of transmission of the organism, may have led to more disease.

b) Bacteriology and Ecology

Legionella species which cause human disease belong to the family, Legionellaceae, which is widely distributed in natural and man-made waters (Fliermans, 1984). At the time of writing (August 1989) details of

33 species and 22 subgroups have been published and most have been shown to be pathogenic (personal communication, Dr R J Fallon). *L pneumophila* is the commonest cause of infection and of its 14 serogroups, serogroup I accounts for most (85%) cases (Reingold et al, 1984).

The bacillus is gram-negative, flagellated, 0.3 to 0.7 microns wide and 1 to 3 microns long (but has filamentous forms), aerobic, and does not form spores (Industrial Water Society, 1985; Bartlett et al, 1986). It can survive temperatures of 60°c and more though only for short periods (Bartlett et al, 1986). Replication occurs at 20 to 45°C and is optimal at approximately 35°C. The virulence of organisms grown at 25°C is higher than that of organisms grown at 41°C (Edelstein et al, 1987a). Growth occurs only in the pH range 5.5 to 9.2 and is optimal in the middle of this range (Wadowsky et al, 1985; States et al, 1987). The presence of L - cysteine and soluble iron are necessary for multiplication in culture.

The organism is fastidious in the laboratory and requires special media for growth; buffered charcoal yeast extract agar (BCYE) is the recommmended medium (Eldelstein, 1987b). By contrast, the organism grows easily and survives well in its natural habitats. It has been postulated that its symbiotic relationship with higher order unicellular organisms such as blue-green

algae and amoebae explains this paradox (Tison et al, 1980; Fliermans, 1984; Rowbotham, 1984 and 1986; Spriggs, 1987) and the presence of both legionellae and amoebae in cold, hot and whirlpool water has been demonstrated (Henke and Seidel, 1986). This may also explain the resistance of legionellae to chlorination and perhaps survival in soil. Water from streams, rivers, puddles, mud, hot spring spas (Bornstein, 1989), coastal sea-water (Ortiz-Roque and Hazen, 1987), and even rainwater (Turner et al, 1984) has yielded legionellae. Apparently, infection linked to legionellae from such sources is rare, though recently Legionnaires' Disease was reported to follow immersion in a river (Farrant et al, 1988).

Man-made reservoirs of water, especially those holding warm, recirculated or stagnant water commonly harbour legionellae. Thus, wet-type air-conditioning and other cooling systems (Fraser, 1984a), whirlpools (Groothius et al, 1985), fountains (Desplaces et al, 1984), calorifiers and particularly electric water heaters (Canada Diseases Weekly Report, 1984; Witherell et al, 1988) and sludge from these sources are important ecological niches for legionellae (Fliermans, 1984). However, the organism is not easily cultured from mains water (Seidler, 1984; Colbourne and Trew, 1986) or from the faucets in private homes (Witherell et al, 1988) but this may reflect low bacterial concentrations. The view that organisms are present in most natural waters

fluorescent antibody technique, legionellae of the OLDA sub-type were found in 12% of mains waters in London (Colbourne et al, 1988a). Heat-shock, whereby the temperature of cold water is raised for some minutes prior to attempts to culture, leads to a higher yield of positive culture (Colbourne J, Lecture at European Working Party Meeting on Legionella, July 1989).

Legionellae are easily cultured from hot water systems. A national survey of 180 hotels and hospitals in England and Wales showed the presence of the organism in between one-half and two-thirds of establishments (PHLS, 1985a). Most isolates were subgroups which cause disease infrequently. Among water characteristics associated with legionella culture were high electrical conductivity and chloride content, and alkalinity. Legionellae have been grown, though rarely, from chlorinated water (Hsu et al, 1984). Vickers and colleagues (1987) reported an association between contamination of hospital water systems and use of river water, increasing hardness of water, use of vertical and old hot water tanks, temperatures in calorifiers of less than 60° and lack of maintenance.

Failure to culture the organism is not proof of its absence. Also, the presence of organisms does not necessarily imply a health hazard, particularly as sub-

groups of low virulence are usually found eg OLDA strains (Watkins et al, 1985; Tobin et al, 1987).

Legionellae survive extremely well in water. In one study tap water at 4°C supported organisms for over one year (Skaliy and McEachern, 1979) and in another, legionellae colonised and thrived in an experimental hot water system with no added nutrients (Schofield and Wright, 1984; Schofield and Locci, 1985b). Water stored in darkness from this system yielded legionellae on culture after 14 months (Schofield, 1985a). Wadowsky and colleagues (1988) prepared cultures of *L pneumophila* from tap water, filtered the cultures using one micron pore membrane filters, and reincubated the filtrate in sterile tap water. *L pneumophila* in the filtrate failed to grow, but did so when incubated with amoebae. In contrast, Legionellae survive drying relatively poorly, being more sensitive than *E coli*, *S aureus*, and *P aeruginosa* (Katz and Hammel, 1987).

c. The Clinical Picture

Prompt diagnosis is important for two reasons. Firstly, investigation of the source of infection may allow early termination of an outbreak. For example, in the outbreak at the Glasgow Royal Infirmary a case had occurred six weeks before the main cluster of cases but was not recognised until retrospective studies took place; early recognition might have led to preventative

action (Timbury et al, 1988) Secondly, appropriate treatment of patients reduces the mortality rate (Bartlett et al, 1986: 58) and may reduce long-term disability.

Unfortunately, the clinical features are not diagnostic. The patient typically presents with non-specific symptoms such as malaise, fever (which is more than 39.5 degrees centigrade in more than two thirds of cases), headache and myalgia (Beatty, 1984; Bartlett et al, 1986). Pneumonic symptoms follow: cough, breathlessness and chest pain. Sputum is often scanty as the bronchioles and alveoli are mainly affected, not the bronchi or trachea.

Multisystemic disturbance is common e.g. gastro-intestinal disturbances such as diarrhoea and vomiting, and neurological changes such as confusion and cerebellar ataxia (Maskill and Jordan, 1981; Weir et al, 1982; Woodhead and Macfarlane, 1985a). The multisystem involvement has been ascribed to toxins but these have not yet been characterised (Edelstein and Meyer, 1984). However, a protease isolated from *L pneumophila* caused haemorrhagic pneumonia in guinea-pigs and may be important in human disease (Baskerville et al, 1986).

Multiple abnormalities are demonstrable by laboratory tests but, with the exception of bacteriology,

are not specific to Legionnaires' Disease. The chest x-ray shows patchy infiltrates or lobar consolidation and these changes are slow to resolve, probably because of fibrosis. A notable feature is the deterioration of the chest x-ray after presentation of illness (Bartlett et al, 1986: 44). Blood biochemistry is usually deranged and the notable changes are hyponatraemia, hypophosphataemia, a rise in the hepatic enzymes, and a raised creatinine phosphokinase. The main haematological change is a neutrophil leucocytosis which may be moderate (Beatty, 1984; Bartlett et al, 1986).

The diagnosis is made on the basis of clinical, epidemiological and microbiological investigations (see later). All the current microbiological diagnostic methods have one or more of the following weaknesses: low sensitivity, non-availability, technical difficulty and delayed results (Edelstein, 1987). Hence, there has been vigourous debate as to whether the diagnosis can be made on clinical grounds.

Emphasis has been placed on the neurological features (Weir et al, 1982), the flushed facies and paroxysmal cough (Beatty, 1984), the relative bradycardia in the presence of a high fever (Bartlett et al, 1986), the biochemical abnormalities, particularly hyponatraemia (Yu et al, 1982) or a combination of the above. Several studies have concluded that Legionnaires' Diseases cannot

be differentiated accurately from other pneumonias on these grounds (Tsai and Fraser, 1978; Macfarlane et al, 1982a; Yu et al, 1982; Woodhead and Macfarlane, 1987). The methods of these clinical studies could be criticised, for example on the small numbers studied, selected groups,and the lack of matching of controls for age, sex and severity of illness, but the conclusion is likely to be correct i.e. the diagnosis cannot usually be made on clinical evidence alone. Nevertheless, when suspicion is high, particularly in the presence of an outbreak, these signs may alert the clinician to the diagnosis.

The outcome of the illness depends on several factors such as the age of the patient and his general health status. Overall 10 to 25% of patients die (Edelstein and Meyer, 1984; Beatty, 1984) but the mortality may approach 80% for the immuno-compromised and 10% or less for the previously well (Bartlett et al, 1986: 60). Long-term respiratory and neurological disability occurs (Lattimer et al, 1979) but its frequency remains incompletely documented. Marrie and colleagues (1981) found that chest x-ray pneumonia change took much longer to resolve for Legionnaires' Disease (8 cases, mean = 69 days) than for other atypical pneumonias (19 cases, mean = 16 days). Early, appropriate treatment reduces the risk of death and perhaps disability. The antibiotics of choice on the basis of

clinical experience are erythromycin and rifampicin. These are not routinely used for either pneumonia or influenza, the two diagnoses usually reached on clinical grounds (Fraser et al, 1977; Beatty, 1984), so some clinicians have argued for the routine use of erythromycin in undiagnosed pneumonia (Connolly and Harrison, 1985; Woodhead and Macfarlane, 1985b). This may be good advice for places where Legionnaires' Disease is relatively common but may be inappropriate where it is rare.

d. Non-pneumonic Legionellosis - Pontiac Fever

While pneumonia is a characteristic of Legionnaires' Disease, infection by legionellae may be manifest in other ways (Woodhead and Macfarlane, 1985a). Occasionally, a severe non-pneumonic illness with some of the other signs and symptoms of Legionnaires' Disease is seen. It may be that sub-clinical pneumonia is present but not demonstrable by diagnostic methods (Frenkel, 1988; Winn 1988b). Local infection e.g. skin abscess and pericarditis, can also occur (Woodhead and Macfarlane, 1985a). The commonest form of non-pneumonic Legionellosis is Pontiac Fever.

In 1968 employees and visitors (including the team investigating the outbreak!) to the County Health Department, Pontiac, USA, developed an illness characterised by malaise, high fever, headache, myalgia,

chills, chest pain, diarrhoea and vomiting, and neurological disturbance (Glick et al, 1978). Retrospective study showed this illness, which had a symptom complex similar to Legionnaires' Disease, to be due to *L pneumophila* serogroup I. In contrast to Legionnaires' Disease Pontiac Fever has a short incubation period (an average of 36 hours), is not a pneumonia, has an attack rate of about 95%, and is self-limiting.

Investigation at the time of the outbreak had shown that the causative agent, then unknown, was associated with aerosol from an evaporative condenser (see also table 2.6). Pontiac Fever outbreaks have given valuable information on the aerosolisation and dissemination of legionellae from evaporative condensers and whirlpool spas (Glick et al, 1978; Groothius et al, 1985a; Mangione et al, 1985; Goldberg at al, 1988). In Pontiac Fever, culture of organisms has been from environmental sources, but not from patients (Fallon, 1986a). When tested on a guinea pig experimental model an isolate from a Pontiac Fever outbreak showed equal virulence to that of organisms associated with the Philadelphia outbreak (Huebner et al, 1984). Legionnaires' Disease and Pontiac Fever cases have also been associated with the same point source (Girod et al, 1982). The question of how the same organism causes two distinct illnesses

remains unanswered except in terms of host susceptibility and size of infecting dose (Rowbotham, 1986).

Rowbotham has argued that Pontiac Fever is an immunological reaction like humidifier fever and that the illness results on exposure to acanthamoebae containing legionellae. As immunological sensitivity to the ubiquitous acanthamoebae is probably common, re-exposure to the combined amoebae and legionellae package may result in a hypersensitivity reaction to the amoebae and a partial infection by the legionellae (Rowbotham, 1980, 1981, 1984 and 1986). That some people developed the illness a second time on re-exposure to the source (Glick et al, 1978) is supportive of this hypothesis.

As well as being important in the study of the transmission of legionellosis, Pontiac Fever is important epidemiologically: it may account for the high prevalence of antibody in some communities (Bartlett et al, 1986:49).

e. Microbiological diagnosis

There are six main bacteriological methods for diagnosing Legionnaires' Disease: light and electron microscopy, culture, the examination of tissue specimens by fluorescence antibody tests, detection of antigen by other means, nucleic acid analysis using DNA probes and the most widely used technique, serology. Each has its

strengths and weaknesses but no one technique is sufficient.

Microscopy can be performed on sputum and other material e.g. lung tissue and bronchial aspirates, but has limited value. The sputum in Legionnaires' Disease is scanty, mucoid and has few pus cells. Monocytes may predominate, in contrast to pneumococcal pneumonia. The absence of gram-positive cocci on a slide smear may help in diagnosis. Staining may show gram-negative coccobacilli with non-parallel sides and tapered ends (Bartlett et al, 1986: 75). If legionellae are present in large numbers then electron microscopy may be considered for more detailed characterisation. Legionellae are found rarely, if at all, in the normal oropharynx (Bridge and Edelstein, 1983) and hence presence of typical organisms on slide smears is noteworthy (but not diagnostic).

Diagnosis by culture of the organism is the 'gold' standard by which other tests are evaluated. No unequivocal false-positive results have been reported (Edelstein, 1987b). In the Philadelphia outbreak the organism was isolated after much difficulty by intraperitoneal inoculation of guinea pigs followed by incubation of spleen suspension into the yolk sac of fertile hens eggs (McDade et al, 1977). Subsequently, techniques have improved greatly but while specificity is

100%, sensitivity of culture ranges from 50 to 80% (Winn, 1988a). Organisms may also be cultured from non-respiratory sites, though this is unusual. The culture medium presently advocated is buffered charcoal yeast extract (BCYE) supplemented with alpha-ketoglutarate and made selective as necessary by the addition of a number of antibiotics (Edelstein, 1987b). Legionellae will not normally grow without L-cysteine, in itself a helpful observation. Edelstein states that with optimal techniques legionellae can usually be isolated from sputum (Edelstein, 1987b). As the average time for growth from clinical specimens is 3 to 4 days, this diagnostic technique may give a result sooner than serology. However, a negative result cannot be inferred for at least two weeks as organisms may grow slowly. Only when diagnosis by culture is given a high priority and high quality specimens such as respiratory secretions obtained by transtracheal aspiration or lung biopsy does the yield exceed 50% (Zuravleff et al, 1983).

The organism obtained on culture is identified by the morphology of the colonies and fluorescence staining characteristics of the colonies. Other techniques including biochemistry may also be applied. The great advantage of culture is that the organism can be subtyped and compared with environmental isolates (see also section 2 e part III) and those from other patients, and hence help in tracing the source of infection

(Watkins et al, 1985; Edelstein et al, 1986). Fatty acid analysis, monoclonal antibody typing, plasmid analysis and DNA analysis are among the specialised techniques available for such investigation (Ketel et al, 1984; Watkins et al, 1985; Edelstein et al, 1986). Further, culture is the only unequivocal means of diagnosis of infection by non-*L pneumophila* species (Taylor, 1987). For these and other reasons Edelstein (1987) has strongly advocated culture and has argued that it is the most sensitive test. In practice, diagnosis is infrequently made on culture partly because some laboratories do not do legionella culture and partly because they do not consider this diagnosis when handling specimens from patients with pneumonia (Perry et al, 1988). Also, satisfactory sputum specimens may be difficult to obtain.

The detection of antigen is a promising approach for many infections including legionellosis (Manek and Wise, 1986). Antigen may be demonstrated in specimens using direct or indirect immunofluorescence techniques. The overwhelming benefit of these techniques is the immediacy of the diagnosis which can be particularly useful in outbreaks (Winter et al, 1986) and the high specificity (approaching 99.9%) but there are several disadvantages: low sensitivity (25 to 50%), technical difficulty, easy contamination of reagents with environmental organisms

and cross-reactions with other bacteria (Edelstein, 1987b).

Legionella antigen can be detected in urine by radioimmunassay, enzyme immunoassay and latex agglutination between one and three days after infection but it may persist for long periods (Bibb et al, 1984; Kohler et al, 1984). The sensitivity may be as high as 80% and the specificity almost 100% (Winn 1988a, Edelstein, 1987b). When marketed this test is likely to have wide application (Edelstein, 1987b).

The promised revolution in the diagnosis of Legionnaires' Disease by the nucleic acid probe for detection and quantification of legionellae (Kohne et al, 1984) is unlikely to occur (Winn, 1988a). Its sensitivity was 57% to 74% when tested against frozen clinical specimens from which legionellae has been isolated; comparable to the direct fluorescence antibody test.

The detection of serum antibody remains the mainstay of diagnosis in Britain and in many other countries (Perry et al, 1988). Yet the criticisms of this method are many (Edelstein, 1987b) and include these: the sensitivity of the method is approximately 75% even when serum collected serially over 6-9 weeks are tested; only 20-40% of patients develop diagnostic changes in titre

within a week of onset of illness (Zuravleff et al, 1981) and the delay in seroconversion may mislead; late positives are of academic rather than clinical value; seroconversion may be even slower in community-acquired cases (Monforte et al, 1988); seroconversion may be missed unless the antigen pool used contains all pathogenic species; and specificity is between 96% and 99% (depending on the number of antigens used in the test material) leading to false positive results especially in patients with cystic fibrosis and tuberculosis; antibody may persist for years and a high static titre may reflect past infection (Plouffe and Baird, 1984; Kallings et al, 1984a). Furthermore, the test has undergone rigourous validation only with *L pneumophila* of serogroup I (Fallon and Abraham, 1982; Taylor, 1987). These criticisms apply to the indirect fluorescence antibody test (IFAT) which is most commonly used, the micrcagglutination test and the ELISA method (Edelstein, 1987b). Winn (1988a) recognises most of these criticisms but quotes the work of Wilkinson and colleagues who found the specificity to approach 100% (1979, 1982). Harrison and Taylor (1987 and 1988) also found the sensitivity and specificity to exceed 80% and 99% respectively. Despite its faults, serology has played a dominant role in diagnosis and will probably continue to do so. The technique is widely available, there are established criteria for interpretation of results, a diagnostic titre may be found on admission in a substantial minority of patients,

elevated non-diagnostic titres in other patients can help in making the diagnosis, and serum is readily available, easily transported and often obtained for other diagnostic tests. Furthermore, most clinicians are familiar with the strengths and weaknesses of the method. Lastly, the earlier fears of false positive reactions in the presence of other infections such as plague, tularaemia, leptospirosis (Tsai and Fraser, 1978) psittacosis, mycoplasma pneumonia (Fallon et al, 1979) and staphylococcal diseases (Glupczynski et al, 1982) were exaggerated. In populations where the prevalence of antibody is low, antibody tests are of undoubted epidemiological and clinical value.

The antibody test result must be interpreted together with the clinical history even though asymptomatic or mild infection may be missed (Frenkel, 1988; Winn 1988b). Where Legionnaires' Disease has been suspected at a late stage, the persistence of antibody is a distinct advantage. The presence of IgM, suggests recent infection but the presence of IgG alone occurs (Bartlett et al, 1986). A complicating factor is the development of an antibody response to several *legionella* subgroups or species (Kallings et al, 1984b; Pelaz et al, 1987; Fallon and Johnson, 1987). While this may result from dual infection (Horbach, 1988) it may be that several subgroups or species have antigens in common (Bartlett et al, 1987; 83). Host factors probably

determine the antibody response rather than the organism (Fallon and Johnston, 1987). When the size of the antibody response does not help differentiate the likely causative organism cross-absorption tests can be done (Fallon, 1986a; Pelaz et al, 1987).

In Britain,using the formolised yolk-sac or heat-killed antigen and the indirect immuofluorescence test, a four-fold rise in antibody titre to 64 or more, or a static titre of 256 or more, together with an appropriate clinical history, provides strong evidence of legionellosis (Fallon and Abraham, 1982b; Taylor, 1987; Harrison et al, 1987) A more detailed discussion of this point is in part 2 b. For other types of antibody tests the diagnostic levels differ but the principles are the same.

None of the tests in use are ideal and the development of a rapid, accurate test is a research priority (Committee of Inquiry, 1987).

PART 2 EPIDEMIOLOGY OF LEGIONNAIRES' DISEASE

(a) Introduction

Epidemiology is the study of the pattern of diseases with the objective of understanding their causes, mode of transmission and relative importance. The description of the frequency of disease over time, by place and by the personal characteristics of patients is the core of

epidemiology. The demonstration of variation in frequency by time, place or person indicates that either there is genetic heterogeneity, or the disease is of environmental origin. If the latter, variation indicates that either exposure to the cause is unequal or host susceptibility differs.

Essential to epidemiological investigation is a definition of the disease, a valid means of diagnosis and an effective surveillance system. The means of diagnosis has been considered earlier, hence, this chapter starts with discussion of the definition of Legionnaires' Disease followed by a description of the frequency of Legionnaires' Disease by time, place and person. The cause of Legionnaires' Disease is unequivocal and is not discussed further. However, the transmission of disease and the relative importance of the reservoirs of infection are reviewed particularly in regard to outbreak and sporadic infection.

(b) Definitions

No single definition of Legionnaires' Disease is universally accepted and many studies apply their own definitions. In the absence of pathognomonic clinical signs and tests which are fully sensitive and specific, definitions must be based on clinical and microbiological findings, and when relevant, epidemiological observation.

In the Philadelphia outbreak the aetiology was unknown and Legionnaires' Disease was defined on the basis of epidemiological and clinical criteria as, "an illness characterised by cough and fever and either a temperature exceeding 38.9°C or any fever and chest x-ray evidence of pneumonia, together with attendance at the American Legion Convention, or exposure to Hotel A" (Fraser et al, 1977). Serological tests were not part of the definition.

With the introduction of serological tests, stricter and more complex criteria have evolved. There is general agreement on the definition of infection with *L pneumophila* serogroup I based on guidance from the Centres for Disease Control. Essentially, it consists of a history of febrile illness with clinical and radiological evidence of pulmonary consolidation and either a four-fold rise in antibody titre to 128 or more, or a static titre of 256 or more to killed antigen. Other laboratory evidence, particularly culture or DFA positivity adds weight to the diagnosis. In practice this, or adaptations of this definition, are usually used for *L pneumophila* infections by all serogroups.

Yu and colleagues (1982) based their definition on CDC criteria except that a static titre of 128 or more was accepted as evidence of Legionnaires' Disease in the presence of undiagnosed pneumonia; they commented that

only 2.6% of 800 consecutive patients had a titre exceeding 128. In England the formalised yolk-sac antigen was found to be highly specific and a four-fold rise to a titre of 64 together with appropriate clinical findings was considered evidence of Legionella infection (Taylor et al, 1979). Less than 1% of the population of England and Wales had titres of greater than 64 to this antigen (Bartlett, 1986; 124). This finding emphasises that the diagnostic or "cut-off" value should be determined on the basis of the prevalence of antibody in the healthy population together with the specificity of the test. The risk of false-positives needs to be balanced against that of false-negatives. Bartlett and colleagues demonstrated the problem of low sensitivity of tests in their study of 59 cases of pneumonia associated with a Spanish Hotel. In only 25 was there laboratory evidence of Legionella infection, despite the epidemiological evidence that some of the other pneumonias were also Legionnaires' Disease (Bartlett et al, 1984b).

While the clinician managing a patient needs to apply strict criteria to ensure that serological evidence is not indicative of past infection and leading him to wrong treatment (Edelstein, 1987b) the epidemiologist may use a wider definition particularly when investigating an epidemic. Bartlett writes,

"In small outbreaks the inclusion of clinical as well as laboratory confirmed cases may help initially by increasing the number of subjects in the investigation and thus improving the statistical power in analytical studies, thereby facilitating the demonstration of an association with an environmental source. In these circumstances the analysis should be repeated when case-searching is completed, and if there are sufficient cases, using only those having both clinical and laboratory evidence of infection" (1986; 125).

In the context of an outbreak investigation, a single titre of 128 and the presence of a compatible clinical picture is, according to Bartlett and colleagues, indicative of recent legionella infection (1986; 124).

The above criteria have been validated for *L Pneumophila* serogroup I but not other subgroups (Edelstein, 1987b). In practice the same criteria have been used but, arguably, this is incorrect (Harrison et al, 1987). Culture of organisms is required to diagnose, with confidence, legionella infection with non-*L pneumophila* species (Taylor, 1987; Edelstein, 1987b). As a consequence most cases of diagnosed Legionnaires' Disease are due to *L pneumophila* of serogroup 1 (Reingold, 1984) but non-*L pneumophila* infections, in particular, are probably underdiagnosed (Swinburne et al, 1988) as they do not meet accepted definitions.

Only exceptionally do case definitions explicitly mention the role of culture and the direct immunofluorescence antibody test (e.g. Yu et al, 1982; Neill et al, 1985) but as the specificity of these tests approaches 100% it is implicit that, together with a compatible clinical history, a positive result is usually diagnostic. Complex definitions involving minor and major clinical signs, as used by Brennen and colleagues (1987), seem unnecessary and have not been widely applied.

(c) Person: characteristics of cases

Personal risk factors have been well defined but remain poorly understood. In outbreaks the overall attack ratio for Legionnaires' Disease is between 0.2 to 2% of those exposed (Fraser et al, 1977). Thus, most people are apparently not susceptible. Yet, in many places including Britain few people have serum antibodies to legionellae (see section e, part i, prevalence). Men are two to three times more likely to be affected as women (Broome, 1984) but the reason is unknown; the two principal hypotheses are that the gender variation is either related to exposure to sources of infection or to differences in susceptibility. While the frequency of most forms of pneumonia rises with age, for Legionnaires'

Disease the risk is greatest at 50 to 70 years (Public Health laboratory Service, 1985b; Broome, 1984; Edelstein and Mayer, 1984). Again the explanation remains obscure but may relate to exposure to the source of infection rather than susceptibility. Children are rarely affected (Bartlett et al, 1986:46) and the argument that the low incidence might result from insufficient testing (Fumarola et al, 1983) is unlikely to be correct. Serological evidence of past exposure, as found by Fumarola and colleagues, is not necessarily indicative of clinical infection and in some cases the antibody in the serum of children with cystic fibrosis may reflect cross-reactions to other gram-negative organisms

Cigarette smoking, alcohol consumption and immunosuppression due to chronic disease or drugs are strongly associated with Legionnaires Disease (Storch et al 1979; England et al, 1981; Broome, 1984; Guiget et al, 1987). Presumably susceptibility to disease is increased and hence the infective dose of organisms is smaller. The higher mortality among such cases supports this hypothesis. Alternatively, the pathway of infection may differ. For example, the immunosuppressed are at high risk of nosocomial infection. This may be a combination of their higher exposure to hospitals (see also "place"), increased susceptibility, and exposure to procedures (e.g. bronchoscopy) and therapies (e.g.

nebulisers) which introduce organisms to the respiratory tract.

Exposure to hospital is a risk factor. Hospitals provide many niches for legionellae: complex hot water systems, cooling towers, whirlpool spas, swimming pools, and nebulisers. They are heated 24 hours of the day and cold water may be warmed and add to the difficulties of controlling the growth of legionellae. However, while water at dental stations in a London Dental Hospital was contaminated with legionnellae, and aerosols were formed by dental drills, there were no associated cases (Oppenheim et al, 1987); a striking example of the observation that environmental contamination does not equate with infection. However, Fotos and Colleagues reported a higher prevalence of anti-legionnella antibody among dental clinic personnel then among controls (1985).

Travelling is an important risk factor. Approximately one third of the cases in England and Wales (PHLS, 1985b) had travelled abroad just prior to their illness. The corresponding proportion in Scotland may be lower (Fallon, 1986b) but the difference may relate to the methods of surveillance. One explanation for this risk factor is that infection arises during exposure to hotels. Several studies have shown this to be so (Grist et al, 1979; Bartlett et al, 1984b). However, the source is usually not identified and the possibility of

infection in aeroplanes, railways, or at other sites needs to be explored. Studies to determine whether the risks are greater when travelling in particular countries have not been published but data presented by Dr C. Bartlett suggests that this is the case (Lecture to the 1989 Spring Meeting of the British Society for the Study of Infection). The large numbers of cases associated with Southern Europe partially, but not wholly, reflect the greater number of travellers going there. More studies relating the numbers of cases arising in each country to the numbers of travellers are needed. To date, attention has focussed on travel abroad, but travel within a country may also be important.

Occupation, social class and ethnicity have not been clearly associated with Legionnaires' Disease (Bartlett et al, 1986: 128). Occupation appears to have an important role but the evidence is fragmentary. Working with the construction industry was associated with sporadic Legionnaires' Disease in the USA (Storch et al, 1979; England et al, 1981). However, Snowman and Colleagues (1982) reported that antibody titres to *L pneumophila* serogroup 1 and 2 were higher in outdoor workers, mainly involved in building, than in indoor white collar workers. An outbreak affected six of 2500 construction workers (three electricians, one fitter's mate, one craft attendant and a labourer) building a power station at a site with four cooling towers (Morton

et al, 1986). Three miners at a Welsh colliery developed Legionnaires' Disease but the source of infection was not located (Davies et al, 1985). Ten men exposed to aerosol while cleaning a steam turbine condenser developed Pontiac Fever (Fraser et al, 1979) and two men cleaning out a cooling tower became ill, one with Legionnaires' Disease, the other with Pontiac Fever (Girod et al, 1982). Surprisingly, Goldman and colleagues reported that the age and sex adjusted prevalence of antibody (IFAT $\geqslant$ 128) was no higher among 48 employees of a Company which serviced cooling towers in New York than in a group of people having pre-marital screening (1980). They also reported that prevalence of antibody ($\geqslant$ 256) among employees in a high risk category responsible for cooling tower maintenance was 16% and not statistically different from that in low risk employees (8.7%). However, the authors conclusion of 'no difference' may have been a type II statistical error resulting from the small numbers in their study. Also, it is notable that ether-killed antigen was used to prepare reagents for the antibody test; such antigen has been shown to be unsatisfactory (Wilkinson, 1979). Working in a hospital is a risk factor. A previously healthy medical registrar (Timbury et al 1986), a consultant anaesthetist, a nurse and a domestic working in Glasgow hospitals developed Legionnaires' Disease and two of them died (unpublished observations).

From these data, we can infer that workplace is important in determining risk of infection but generalisations cannot be made. The presence of a cooling tower at work may be the important factor rather than the type of work. The question "Where do you work?" is clearly an important part of the clinical history of pneumonia (Zumla et al, 1988) not only to identify outbreaks but also to ascertain whether a cooling tower is present at the workplace.

Other risk factors include asthma, perhaps relating to hospitalisation, use of aerosols and steroids (Beer S et al, 1985); sleeping next to a window (Thacker et al, 1978; Ad hoc Committee, 1986) and showering first thing in the morning (Bartlett et al, 1984).

Studies of the association between Legionnaires' Disease and social class have apparantly not been published. Storch and colleagues found an association between being black and Legionnaires' Disease but concluded that this was probably an artefact (1979).

The personal risk factors for sporadic cases are little different to those of outbreak cases (Storch et al, 1979; England, 1981). However, fewer sporadic cases have a history of underlying disease.

The risk factors discussed above are associations and have often not been studied rigourously enough to demonstrate cause and effect. For example, Storch and colleagues (1979) considered both the effect of multiple comparisons and interactions between associations. They used a linear logistic model to study the interaction of 10 variables (including smoking and drinking alcohol) associated with Legionnaires' Disease. However, their paper does not indicate that either age or gender were included. Since these factors are likely to interact with both the ten variables studied and the disease the validity of the analysis is questionable.

(d) Time: secular trends, seasonal variation and the epidemic curve

Three aspects of the relationship between disease and time may yield information about the causal pathway, mode of transmission of disease and its natural history: trends over long periods of time (secular trends), seasonal and other cyclical fluctuations and the epidemic curve.

Knowledge of the secular trend of Legionnaires' Disease is extremely limited. The modern environment with its air conditioned large buildings, cooling towers, spas, and many other sources of aerosolised warm water provides an ecological niche where legionellae can thrive and brings together the agent and host. One would

predict that Legionnaires' Disease has become commoner but there is no solid evidence to support the prediction.

In a retrospective serological survey of 500 pneumonia patients treated in Seattle, USA between 1963 and 1975 all five cases of Legionnaires Disease occurred after 1970 (Foy et al 1979). The small number of cases and non-availability of many early sera preclude conclusions about time trends. A retrospective study of 3027 autopsies on fatal pneumonia cases in a German hospital between 1969 and 1985 is of interest (Schurmann et al, 1988). The numbers and proportion of cases which were due to Legionellosis is shown in table 2.I. The proportion of cases due to Legionnaires' Disease was greater in the period 1978 to 1985 than before i.e. 4.3% (57/1318) of pneumonia compared to 1.9% (32/1709) cases (x^2=15.6, df=1,P<0.001). However, this finding needs to be cautiously interpreted as: 1) the earlier specimens (pre 1977) had undergone different staining treatment from later ones and this may have affected interpretation; 2) the policy for autopsy had apparently altered (a steady decrease in the number of autopsies from 1102 in 1969 to 573 in 1985) perhaps causing selection bias e.g. towards nosocomial pneumonias; 3) most cases were nosocomial hence the data are not applicable to the general community. Of interest, however, is the considerable year-to-year variation

TABLE 2.1

LEGIONNAIRES' DISEASE OVER 1969-1985 IN AUTOPSIED PATIENTS IN A GERMAN HOSPITAL

Year	Autopsies	Pneumonia (%)	Legionella pneumonia (% of pneumonia)
1969	1102	211 (19.1)	4 (1.9)
1970	978	126 (12.9)	3 (2.4)
1971	896	126 (14.1)	2 (1.6)
1972	978	212 (21.7)	3 (1.4)
1973	889	234 (26.3)	4 (1.7)
1974	882	186 (21.1)	3 (1.6)
1975	793	204 (25.7)	3 (1.5)
1976	824	196 (23.8)	4 (2.0)
1977	809	214 (26.5)	6 (2.8)
1978	703	143 (20.3)	9 (6.3)
1979	601	174 (29.0)	9 (5.2)
1980	600	168 (28.0)	4 (2.4)
1981	586	182 (31.1)	5 (2.7)
1982	547	154 (28.0)	4 (2.6)
1983	626	168 (26.8)	10 (6.0)
1984	562	177 (31.5)	12 (6.8)
1985	573	152 (26.5)	4 (2.6)
Total	12949	3027 (23.4)	89 (2.9)

(range = 1.4% to 6.8%) in the proportions of cases which were DFA positive.

Fluctuation in the annual number of cases probably occurs but, as shown in table 2.3 (p 53), there was no clear evidence of this in the USA or England and Wales (but local variation may have occurred). In Scotland, there was marked annual variation in the period 1978-1986. Striking year-to-year variation apparently occurred in Finland too, e.g. two cases in 1981, 36 cases in 1983 and 10 cases in 1985 (Jousimes-Somer,data presented to European Working group on Legionella Infection 1986). In the Nottingham area the incidence of Legionnaires' Disease varied from year-to-year and declined after 1980 despite more tests being done (Woodhead et al, 1986 a and b). The explanation for annual fluctuation is unknown but presumably environmental change occurs e.g. in the control measures used in cooling towers and hot water systems, or in the virulence of the organism.

Legionnaires' Diseases is commoner in summer and early autumn and admission of a pneumonia patient at such a time should alert the clinician (Bartlett et al, 1986: 40). The seasonal peak applies to both travel and non-travel associated cases but seems more marked for the former (PHLS, 1985b). The simplest explanation for the seasonal variation is that the organism multiplies faster

in the warmer waters of summer. Alternatively, or additionally, the greater use of cooling towers in summer for air-conditioning may provide opportunities for dissemination. There may be more complex reasons relating to the life cycle of species which grow in symbiosis with legionellae. Rowbotham (1981) speculates that legionellae are digested by amoebae at low temperatures but infect amoebae at about 30 degrees centigrade or more. The warmer cooling tower water of late summer may allow legionellae to become infective and transmissable to humans. Two studies have shown that legionellae are easier to isolate from natural water in summer and autumn rather than winter (Bercovier et al; Tobiansky et al, 1986). The observation by Fliermans (1984) that the number of legionellae rose in association with the degradation of the plant *Myriophillum spicatum* further highlights the complexity of the ecology of the genus.

Climate has been invoked as important in the web of causation of Legionnaires' Disease. For example high winds were associated with the Stafford and Washington outbreaks (Hoyle et al, 1985) and wind direction appeared to determine the distribution of cases in the Dennistoun outbreak in Glasgow (Ad-hoc Committee, 1986). Humidity is important in the survival of all organisms pathogenic to man (Bovallius et al, 1980) and this applies to legionellae. Indeed, legionellae were found to be more

sensitive to drying than *E. coli, S. aureus* and *P. aeruginosa* (Katz and Hammel, 1987). In laboratory experiments aerosolised legionellae survived best at 65% relative humidity (Hambleton et al, 1983). Weather also determines the dissemination and deposition of aerosols. Particles exceeding 0.1 microns rapidly settle but droplet nuclei which are less than 0.1 microns may be suspended in air (Riley, 1980) and carried long distances by air-currents (in particular), diffusion and sedimentation (Bovallius et al, 1980). While weather is apparently important in the Legionnaires' Disease pathway and may explain seasonal variation, its precise role is undetermined.

The epidemic curve in an outbreak, particularly if exposure of cases occurred at a single time and place (point source), may allow estimation of the incubation period and suggest hypotheses as to the source. The range of 2 to 10 days for the incubation period was first derived from the Philadelphia outbreak data (Fraser et al, 1977). Clearly knowledge of the epidemic curve and the incubation period may help link a case to an event, e.g. travel abroad, admission to hospital and shutdown of a cooling tower.

The shape of the epidemic curve may help decide the nature of the source. A rapid rise and fall in the numbers of cases favours a point-source outbreak which,

in the context of Legionnaires' Disease, is characteristic of cooling tower outbreaks (Fraser et al, 1977; Ad hoc Committee, 1986). A "flat" epidemic curve is more typical of outbreaks traced to domestic water systems (Bartlett et al, 1986:125).

In the investigation of the source of infection information on the temporal variation of Legionnaires' Disease must be combined with that on variation by place.

(e) Place

The epidemiological study of place ranges from international comparisons of disease frequency to the examination of the environment of individual cases. While the demonstration that a supposed source of infection does contain the organism is in the realm of microbiology, epidemiology is necessary to link that source to human disease. This section opens with a discussion of geographical variation in the frequency of disease and closes with a discussion of the sources and mechanism of transmission of infection.

i Geographical variation in the frequency of disease

Legionnaires' Disease is found worldwide but most cases have been reported from the industrialised "Western" countries (World Health Organisation, 1982). Whether this merely reflects the availability of diagnostic methods or a higher incidence of disease is

undetermined. As the ecological niches which support legionellae such as, complex recirculating water systems and hot water at 35-55°c, are characteristic of the industrialised environment the incidence in developing countries may be comparatively low. However, in industrialised parts of developing countries Legionnaires' Disease is probably not rare (Ortiz-Roque et al, 1987). Before describing the studies on the frequency of disease, the strengths and weaknesses of the measures usually used i.e. incidence, proportions and prevalence, are discussed.

For comparing acute disease the most valuable epidemiological measure of frequency is the incidence rate. Cautious interpretation of incidence studies of Legionnaires' Disease is essential in view of the difficulties of diagnosis, the specialised nature of laboratory tests and the low sensitivity of the diagnostic methods. Incidence rates tend to underestimate. However, even if the specifity of tests approached 100%, routine testing could lead to false positives outnumbering false negatives and even true positives. A change in incidence over time may be an artefact related to increasing awareness, availability and use of laboratory tests. In the United Kingdom, unlike the United States (Centres for Disease Control, 1988) the disease is not notifiable and incidence data come from voluntary systems of surveillance based mainly

on laboratory reports (PHLS, 1985b). Publicity concerning the disease may alter the likelihood of reporting. Hospital morbidity and mortality data are not of value in estimating the incidence for reasons similar to the above and the fact that there is no specific International Classification of Disease code for Legionnaires' Disease but it is grouped with other gram-negative pneumonias under code 482.8 (WHO, 1977).

Estimates of incidence often derive from local studies. Usually the number of Legionnaires' Disease cases is expressed as a proportion of all pneumonias. This proportion is then applied to national figures on pneumonia and the incidence of Legionnaires' Disease estimated. The pitfalls of this approach are apparent: the local estimate may not apply nationally, the proportion may not apply to other years and, of course, the inevitable problem of insensitivity of tests in establishing aetiology. Even with thorough testing in the context of a research study the causative agent may only be identified in two-thirds of cases of pneumonia, as in the British Thoracic Society Study (1987).

Another perspective on the frequency of disease has been provided by surveys of the prevalence of serum antibody. The problems of interpretation are many. Firstly, antibody persists over long periods (Lattimer et al 1979; Osterholm et al, 1983) yet levels drop by

about 25% over 18 months (Kallings et al, 1984a; Plouffe and Baird, 1984) which means that a point-prevalence rate is neither an indicator of recent infection nor of cumulative incidence. Secondly, prevalence studies do not usually indicate the severity or type of infection e.g. whether subclinical, Pontiac Fever or Legionnaires' Disease. Thirdly, interpretation of the prevalence will depend upon the laboratory techniques used and the level of antibody which is of significance locally. Lastly, there are the methodological problems common to all surveys e.g. representativeness of the sample and selection bias due to the fact that cases may have died or be institutionalised. Nevertheless, prevalence studies are the only means of assessing the number of undiagnosed cases and hence of throwing light on the true dimension of legionellosis.

Few studies on the incidence of Legionnaires' Disease in geographically defined populations appear in the literature. Further, the comparability of the studies is low. Table 2.2 summarises some published data on the incidence of Legionnaires' Disease in several countries; the incidence varied greatly. At the third European Working Group on Legionella Infections meeting in Madrid (1988), figures were presented on the numbers of cases diagnosed in 1987. (I am grateful to Dr R. Fallon for minutes of the meeting). Unfortunately, details of methodology and definitions were not recorded.

TABLE 2.2

REPORTED INCIDENCE OF LEGIONNAIRES' DISEASE IN SEVERAL COUNTRIES

Reference	Country	Time	Details on serology	Estimate of mean annual incidence per million population	Comment
Centres for Disease Control (1988)	USA	1978-1986	CDC reagents	3.0	CDC criteria
Chereshky (1986	N.Zealand	1982-1985	CDC reagents & methods	10.6*	CDC definition
Commitee of Inquiry (1987)	England	1978-1986	Mainly formolised yolk sac antigen to range of antigens as discovered	3.1	Case definition on same principles as CDC guidelines
Fallon (various years)	Scotland	1978-1986	1978- CDC reagents; subsequently heat-killed antigens to range of species and subtypes as discovered	9.5	Case definition similar to CDC guidelines
Greco (1984)	Italy	Jan 1979-Sept 1982	CDC and PHLS reagents Most cases diagnosed on serology.	0.5	108 cases; 32 were clinical diagnoses and single IFAT titre of > 128 accepted. Validity of estimate poor.
Heltberg (1988)	Denmark	Nov 1982-Feb 1985	Heat killed antigen from 13 species or sub-types	2.9*	CDC criteria on serology used. Five cases had no pneumonia; 37 cases were non-pneumophila but diagnosed serologically

* Incidence when the non-L pneumophila cases, with only serological evidence, are excluded. When such cases were included the incidence was 6.0 in Denmark and 28.1 in N. Zealand.

Nonetheless, the following approximate rates per million in 1987 (my calculations) are further evidence of international variation in disease incidence:Austria 1.7; Belgium 4.1; Denmark 14; England and Wales 4.2; France 7.4; Italy 0.4; Netherlands 3.0; Norway 2.9; Portugal 2.8; Scotland 9.2; Spain 3.7; Sweden 1.7; USSR 1.5. Such variation has been noted but not explained (World Health Organisation, 1982) However, in the absence of agreed definitions and laboratory methods, detailed information on the organisation of services, the place of treatment, approach to the investigation of pneumonia, and surveillance methods, conclusions as to the degree or cause of variation cannot be made. Suffice it to say that there is evidence of international differences in the incidence of Legionnaires' Disease.

Table 2.3 compares in more detail the number of cases in the period 1978 to 1986 in Scotland (as reported by the Ruchill Hospital laboratory), England and Wales and the USA. The Scottish data gives an overall incidence of about 9.5 per million residents which varies markedly over time. The rates for the other two countries are about three per million and relatively stable over time. As environmental isolation of micro-organisms in Scotland has been difficult (Jackson, 1985; Bhopal, 1986) and the prevalence of antibody low (Fallon and Abraham, 1982b) the higher incidence rate is unexpected. Perhaps Scottish clinicians were more ready

TABLE 2.3

NUMBER OF CASES OF LEGIONNAIRES' DISEASE IN SCOTLAND, ENGLAND AND WALES, AND THE UNITED STATES OF AMERICA IN THE PERIOD 1978 TO 1986

Year	Scotland[1]	England and Wales[2]	United States of America[3]
1978	20	73	761
1979	35	129	593
1980	31	181	475[4]
1981	20	143	408[4]
1982	32	138	654
1983	52	160	852
1984	114	151	750
1985	98	211	830
1986	26	18	948
TOTAL	428	1368	6271

1. Fallon, annual reports in CDS weekly bulletin and Fallon and Abraham (1982)
2. Committee of Inquiry (1987)
3. Centres for Disease Control (1988)
4. Figures exclude epidemic cases i.e. sporadic cases only

to test for Legionnaires' Disease when managing pneumonia, or disease surveillance was more complete. Alternatively, the higher incidence rate may be real. Within the United States the incidence rate in 1983 varied from State to State; the disease being more common in the North and Mid-West than in the South. Among States where the disease was notifiable the rate varied from less than one case per million to more than five cases per million (Centres for Disease Control, 1984 and1988). This State-by-State variation was also seen for sporadic cases (England et al, 1981).

Studies of Legionnaires' Disease as a proportion of pneumonia have also demonstrated great geographical variation (Annonymous, 1983). Table 2.4 summarises some of these studies. The difficulties in interpretation of such data must not be underestimated and include: 1) The number of patients recruited into many studies was small, e.g. Marrie (1981) reported on 29 patients, Woodhead (1986a) on 42 and Carter (1979) on 47; 2) Few studies span a period of time long enough to avoid the effect of short term changes in incidence, say 5 years or more; 3) The antigens and methods used differ; older studies used fewer antigens than newer ones; 4) Some studies report the proportion of pneumonias which were Legionnaires' Disease in case series where only a fraction of cases were investigated for the disease (Kertulla et al, 1987; Mohammed et al, 1987) and these

TABLE 2.4

STUDIES OF LEGIONNAIRES' DISEASE AS A PROPORTION OF PNEUMONIA

AUTHOR	PLACE	COUNTRY	TIME	METHOD	TYPE PNEUMONIA	ANTIGENS	SAMPLE	POSITIVE	%
ANDREONI (1986)	SEVERAL	ITALY	1985-1986	SEROLOGICAL	ALL	4	355	16	4.5
AUBERTIN (1987)	4 CENTRES	FRANCE	1982-83	IFAT	COMM-ACQU+	12	274	29	10.6
BOUZA (1984)	MADRID	SPAIN	1978-1983	IFAT	ALL	1	750	45	6.0
BRENNEN (1987)	PITTSBURGH	USA	1984-1985	HEAT-KILLED	NOSO++	7	185	26	14.0
BTS (1987)	25 HOSPITALS	UK	1982-83	IFAT+CFT	COMM-ACQU	NS	453	9	2.0
CARTER (1979)	CHICAGO	USA	1979	IFAT	ALL	1	47	11	23.4
FOY (1979)	SEATTLE	USA	1963-1975	IFAT	COMM-ACQU	1	500	5	1.0
FRIIS-MOLLER (1984)	COPENHAGEN	DENMARK	1982-83	RMAT+IFAT	ALL	10	92	25	27.2
KALLINGS (1984b)	STOCKHOLM	SWEDEN	NS	IFAT	COMM-ACQU	4	437	25	5.7
KENNEDY (1983)	GLASGOW	SCOTLAND	1979-1982	IFAT	ALL	0	96	11	11.4
LODE (1984)	UNKNOWN	GERMANY	1980-81	IFAT	ALL	7	110	11	10.0
MACFARLANE (1982)	NOTTINGHAM	UK	1980-81	IFAT	COMM-ACQ	10	127	19	15.0
MARRIE (1981)	HALIFAX	CANADA	1979-80	IFAT	ALL	1	27	8	30.0
MCNABB (1984)	LONDON	UK	1979-1982	IFAT	COMM-ACQ	1	80	0	0.0
ORTIZ-ROQUE (1987)	VARIOUS	PUERTO RICO	1984	DFA	NECROPSY	10	88	13	15.0
RENNER (1979)	IOWA	USA	1972-1977	IFAT	ALL	1	586	24	4.1
SAITO (1984)	6 HOSPITALS	JAPAN	NS	DFA ON LUNG	NECROPSY	7	362	42	11.6
SCHURMANN (1988)	BERLIN	GERMANY	1969-1985	DFA+DIETERLE*	NECROPSY	12	3027	89	2.9
WALDER (1981)	MALMO	SWEDEN	1977-1978	IFAT	NECROPSY	1	112	2	1.4
WHITE (1981)	BRISTOL	UK	1974-80	IFAT	COMM-ACQU	1	210	3	1.4
WOODHEAD (1986a)	NOTTINGHAM	UK	1982-1983	IFAT	COMM-ACQU	NS	42	2	5.0
YU (1982)	PITTSBURGH	USA	1979-1980	IFAT	ALL	4	142	18	12.7**

\+ Comm-acqu=community-acquired
++ Noso=nosocomial
+++ NS=not stated
* Dieterle stain
** This figure is based on confirmed cases.

obfuscate not illuminate; 5) Some studies enrol only community-acquired pneumonias, others nosocomial cases, others report the results of necropsy and most include all pneumonia cases; 6) The not uncommon practice of basing the reported proportion on the number of cases in which a microbiological diagnosis was achieved (Kennedy, 1983; Saito, 1984; Aubertin, 1987) rather than the more appropriate denominator, the number of cases studied, which has been used in the preparation of table 2.4. As such, the proportions in table 2.4 may differ from previous reviews (Bartlett et al, 1986) and from the original reports; 7). The proportion of pneumonias in which a diagnosis is reached has been as high as 97% (MacFarlane et al, 1982b) and as low as 49% (White et al, 1981), which adds another problem of interpretation.

The proportion of pneumonias which were Legionnaires' Disease varied from none in the study by McNabb (1984) to 30% in that by Marrie (1981). Even within each country considerable variation has been reported e.g. 1% in Seattle, USA (Foy, 1979) and 23% in Chicago, USA (Carter, 1979). In Britain, in 80 consecutive pneumonia admissions to a central London Hospital there were no cases of Legionnaires' Disease and only one patient with pneumococcal pneumonia had a static titre of 128 (McNabb et al, 1984) and in Bristol, 1.4% (3/210) of a series of pneumonia admissions from the community were diagnosed as Legionnaires' Disease (White

et al, 1981). Yet the corresponding proportion was 15% (19/127) in Nottingham (Macfarlane et al, 1982b). Even allowing for the fact that legionella serology was available for only 39 of the 75 months of the Bristol study, this is an important difference. When the Nottingham study was repeated (as part of a national study) the proportion had fallen to 5% (2/42) (Woodhead et al, 1986a). Woodhead and colleagues interpreted this as evidence of a decline in the incidence, particularly as the numbers of tests done rose. It is notable however that statistically the two proportions are not significantly different (df=2, chi squared=3.0, $p>0.05$). Woodhead and colleagues also reported that 15 of 50 cases of community-acquired pneumonia admitted to an intensive care unit had Legionnaires' Disease (1985c).

The proportion of pneumonias which were Legionnaires' Disease in Scotland has been reported as 6.7% (Fallon and Abraham, 1982b) and, in a smaller series in an infectious diseases hospital, 20.3% (11.4% using total cases studied as the denominator) (Kennedy and Borland, 1983). The best estimate of the proportion for Britain is 2% and this comes from a study of community-acquired pneumonia admissions to 25 hospitals in 1982/3 (British Thoracic Society, 1987). However, this study relates to a single year.

Similar studies based outside hospitals are few. In Seattle, USA, analysis of 500 stored sera from pneumonia patients in a prepaid medical-care group of whom 84% were out-patients showed that 1% (5 cases, of whom three also had seroconversion to influenza virus) were Legionnaires' Disease giving an extrapolated incidence of 40 to 280 per million residents per year (Foy et al, 1979). However, 24 other patients had legionella titres of 256 or more and the true incidence may have been much higher. Despite its limitations this study has been widely quoted as a measure of the true dimension of Legionnaires' Disease i.e. 25-50,000 cases per year in the USA. In Nottingham (UK) in the period October 1984 to September 1985 there were 236 consecutive community-acquired pneumonias and one (0.4%) was diagnosed as Legionnaires' Disease (a travel associated case) (Woodhead et al, 1986a). Yet, over the 12 year period 1972 to 1984, the same researchers found 90 confirmed cases of Legionnaires' Disease and concluded that 79 were community-acquired and only 7 had returned from abroad. They noted a marked annual fluctuation in number of cases e.g. 4 in 1982 and 1984, and 14 in 1980 (Woodhead and Macfarlane, 1986b). These studies on the proportion of pneumonias which are due to legionellae are intriguing and point to major geographical variations but they shed little light on the cause or meaning of the phenomenon.

Prevalence studies, summarised in table 2.5, also demonstrate variation. In interpreting prevalence studies all of the pitfalls described earlier apply but in addition, there is this: while illness is a prerequisite for inclusion in studies of incidence or in a case-series, prevalence studies are generally of a sample of the normal population and there is no clinical history. Therefore a high titre may indicate any form of legionellosis, asymptomatic exposure or, indeed no exposure at all in the case of cross-reactions. Nonetheless, such studies are important for two reasons. First, they guide as to the potential importance of legionellosis in a community. Second, the proper interpretation of serology results from patients requires knowledge of the antibody titres within the local community. In Scotland only 0.4% of all sera tested from 740 well persons had antibody to *L pneumophila* of serogroup I (Fallon and Abraham, 1982b). In Nottingham and surroundings (UK) 1.5% of residents had antibody levels indicative of past infection (Macrae et al, 1979) and none had a titre of 256 or more. By contrast, the prevalence was higher in most other countries and in subgroups of some populations the prevalence has been extraordinarily high e.g. 64% in aboriginal populations in Australia (Sampson, 1988) and 12.5% in irrigation workers in Israel working with waste-water (Bercovier et al, 1984). Surprisingly, there is no clear evidence that a high community prevalence of antibody is

TABLE 2.5

STUDIES OF THE PREVALENCE OF ANTIBODY TO LEGIONELLAE

AUTHOR	PLACE	COUNTRY	TIME	METHOD	ANTIGENS	POPULATION	SAMPLE	% POS.*
ANDREONI (1986)	SEVERAL	ITALY	1984-1985	NO DETAILS	4	BLOOD DONORS+OTHERS	130	0.0
BORNSTEIN (1986)	LYON	FRANCE	NS	IFAT	13	BLOOD DONORS	583	0.0
BEER (1985)	TEL-AVIV	ISRAEL	1982	IFAT	11	ASTHMATICS	184	17.0
						CONTROLS	80	1.3
BERCOVIER (1984)	30 PLACES	ISRAEL	NS	IFAT	15	IRRIGATION WORKERS	240	12.5
						CONTROLS	72	1.4
BOLDUR (1986)	RAMLE	ISRAEL	NS	IFAT	11	ELDERLY AT 1 INSTITUTION	59	30.5
						ELDERLY AT HOME	26	0.0
BOUZA (1984)	MADRID	SPAIN	NS	IFAT	NS	BLOOD DONORS+STAFF	239	0.0*
COSSAR (1982)	VARIOUS	SCOTLAND	1977	IFAT	1	SCOTTISH TOURISTS	174	9.0
DAVIES (1985)	VARIOUS	WALES	NS	IFAT	1	COAL MINERS	464	0.2***
DENNIS (1984)	UNSTATED	UK	NS	IFAT	1	STAFF IN BUILDING	90	0.0
FALLON (1982a)	VARIOUS	SCOTLAND	1978-82	IFAT	12	SCOTTISH TOURISTS	740	0.4
FOTOS (1985)	W VIRGINIA	USA	NS	ELISA	8	DENTAL HEALTH STAFF	270	20.0****
						CONTROLS	67	8.0****
FOY (1979)	SEATTLE	USA	1963-1975	IFAT	1	PNEUMONIA PATIENTS	500	9.0
GOLDMAN (1980)	NEW YORK	USA	1978-1979	IFAT	1	PREMARITAL SCREENING	720	11.0++
						COOLING TOWER STAFF	21	19.0++
GUO CHEN (1984)	VARIOUS	TAIWAN	NS	RMAT	11	MEN 20-30YR	256	15.0+++
HIGHAM (1985)	RIYADH	SAUDI ARABIA	NS	IFAT	1	BLOOD DONORS (MALES)	200	2.0
MACRAE (1979)	NOTTINGHAM	UK	NS	IFAT	1	ANTENATAL+ SURVEYS	2023	0.0
PITT (1980)	ADELAIDE	AUSTRALIA	NS	IFAT	1	BLOOD DONORS	208	9.6
RENNER (1979)	IOWA	USA	1978	IFA	1	POPULATION 15-64	53	5.7
SAMPSON (1988)	PERTH	AUSTRALIA	1985	IFAT	6	NON-ABORIGINES 20-40	200	2.5
						ABORIGINES (KIMBERLEY)	100	9.0
TIMBURY (1986)	GLASGOW	SCOTLAND	1985	IFAT	1	HEALTHY STAFF	113	1.8**
WENTWORTH (1984)	MICHIGAN	USA	1980-1983	HAEMAGGLUTINATION	10	SCREENING GROUP	1159	7.9+++
YU (1982)	PITTSBURGH	USA	1979-1980	IFAT	4	HOSPITAL PATIENTS	800	2.5**

* Unless stated otherwise, positive refers to a titre of 256 or more or a level of significance relevent to the population concerned as defined by the authors; as such these figures may not match those quoted elsewhere.

** Titre of more than or equal to 64

*** Titre of more than or equal to 16

**** Significantly higher than a known control sample

++ Titre of more than or equal to 128

+++ Titre more than or equal to 16 (said to be equivalent to one of 64 using IFAT)

associated with a high local incidence of clinical disease. Seroconversion could occur after asymptomatic exposure to pathogens of low virulence. For example, Boldur and colleagues (1986) reported that a high proportion of the institutionalised elderly had legionella antibody and demonstrated that seroconversion occurred shortly after admission. By contrast, none of 26 elderly people living in the nearby community had antibody. However, they do not state that those seroconverting were ill. (Hypothetically, such exposure may act as immunisation and protect against severe clinical infection).

Intriguing is the observation of Boldur and colleagues that the prevalence of antibody among wild animals can be as high as 35% (horses) or as low as 0% (laboratory rabbits), yet there is no known, natural animal equivalent of Legionnaires' Disease (1987). Collins (1986) reviewed the literature and concluded that, overall, domestic animals have higher titres than wild animals. He also observed that horses commonly have high titres yet the disease cannot be induced experimentally.

Attempts to explain high local prevalence in terms of environmental factors in the community have seldom been reported for a defined population. The study of irrigation workers in Israel who were working near water

sprinklers is a rare example (Bercovier et al, 1984). While the prevalence amongst workers exposed to waste water was 12.5% (n = 280) and those exposed to clean potable water was 7.2% (n = 81) a control group had a prevalence of 1.4% (n = 72).

While detailed studies of the geography of outbreaks have been reported, there is a dearth of information on the geography (location of residence or workplace) of non-outbreak cases. As noted on page 52 within the United States of America the incidence of Legionnaires' Disease varied from state to state; consistently the highest rates have been in the North and Mid-West (Centres for Disease control, 1984, 1988). Similar variation was observed for sporadic cases only (England et al, 1981). No explanation for these observations was advanced by the authors.

Dournon and colleagues mapped cases of Legionnaires' Disease in Paris by place of hospitalisation but found no clustering (1988). Wentworth (1982) reported no geographical concentration of cases in Michigan.

Though much of the geographical disparity in the frequency of Legionnaires' Disease undoubtedly relates to differences in study populations, laboratory methods, non-systematic testing methods, varying case mixes, and other sources of artefact, overall, the data support the

conclusion that there is striking local and international variation in this disease (Anonymous, 1983).

Legionnaires' Disease is an uncommon pneumonia, though underdiagnosed. However, each nation, region and district needs to consider its own position. Further, generalisations based on whole populations may not apply to subgroups of the population. Lastly, studies to explain variations, as opposed to observe them, are needed.

ii Sources of infection and mode of transmission

Our knowledge of the reservoir of infection and the mode of transmission comes mainly from the study of outbreaks (or nosocomial infection), though the source of many outbreaks remains unknown (Fraser et al, 1977; Eickhoff 1979; Anderson et al, 1985; Helms et al, 1984b). Of the 26 outbreaks listed by Band and Fraser (1982) the source could not be stated for 19. To the end of 1986, 21 outbreaks (excluding travel-related disease) had been recognised in England and Wales but the source of infection was not identified in eight, eight originated in hospitals, three in hotels, one at a power station construction site and one on an industrial estate (Committee of Enquiry, 1987).

The environment of non-outbreak, community-acquired cases is seldom studied. Stout and colleagues

investigated two invalid patients who were housebound for the two weeks prior to developing Legionnaires' Disease (1987). There was no cooling tower near their houses, nor airconditioning within the houses. Water samples from their homes grew organisms which matched isolates from the patients. The authors concluded that these patients were infected from the domestic water supply and emphasised that the risk of such infection may be low but, nonetheless, homes of community-acquired cases need to be investigated. They suggest that 30% of home water systems may have bacteria. However, Witherell and colleagues (1988) grew legionellae in only 2% of water heater samples and in none of 68 samples from other domestic water sources. The observations of Arnow and Neil (1984) are also pertinent. They isolated legionellae in 37% of 52 apartments near Chicago but no residents had had pneumonia and only one person had an elevated antibody level exceeding 256. Redd and Cohen, (1987) commenting on the observations of Stout and colleagues, felt that no microbiological surveys or elimination projects were justified until the mode of transmission of sporadic cases was found.

Though sporadic cases account for 75% of infection little is known about the mode of transmission (Committee of Inquiry, 1987). The assumption, supported by the fact that the personal risk factors and seasonal variation are similar (Storch et al 1979; England et al,

1982; Kuritsky et al, 1984; Helms et al, 1984b),is that the sources of the sporadic cases are similar to those of outbreak cases. Joly and Winn (1984) made the intriguing observation that while isolates from outbreak related cases matched environmental isolates from cooling towers, an isolate from a sporadic case matched isolates from domestic water samples. The current weight of opinion is that sporadic cases mainly occur from domestic water sources and, to date, no other proven source for such cases has been identified.. Clearly this matter needs further study (Bartlett et al, 1986; Redd and Cohen, 1987). The mechanism of transmission needs to be defined.

Outbreaks have been associated with cooling towers, calorifiers and associated plumbing, showers and spas. Nosocomial infection, in addition to the above, has been associated with nebulisers. The above sources are found in industrial complexes, hospitals, hotels, and leisure complexes and outbreaks have usually been traced to such buildings. The common factors have been complex plumbing where water is heated, re-circulation or stagnation of water, and a means of aerosolisation of water. Person-to-person spread has never been satisfactorily demonstrated and only one case report records circumstantial evidence of such a mode of spread (Campbell-Love et al, 1978).

The epidemiological evidence incriminating the above sources of infection is now considered.

Cooling towers

Figure 2.1 illustrates the structure and function of a cooling tower and an evaporative condenser. Essentially, these structures eject heat to the atmosphere by evaporation of water. Steam and water droplets are ejected but most of the coolant water is recirculated (Miller, 1979). The ecological requirements of legionella growth are present: warm water usually at 25 to 29 degrees centigrade, recirculating water, sludge which contains an array of microorganisms and inorganic materials which may support growth. Surveys in several countries have shown that cooling towers are often contaminated with legionellae (Kurtz et al, 1982 ; Tyndall et al, 1982a; Saito et al, 1984; Witherell et al, 1984;). Tyndall and colleagues (1982a) demonstrated, with a validated direct fluorescence antibody test, that most cooling towers had legionellae, and that neither the use of biocides or other factors such as source water could predict accurately the type and concentration of organisms. They found that legionella concentrations rose after cleaning and that the type of organism also altered. Grow and colleagues (1984), studied two cooling towers over nine months. They found that the numbers of viable legionellae fluctuated markedly. Treatment of the tower led to a

Basic Structure of Cooling Towers (left) and Evaporative Condensers (right)

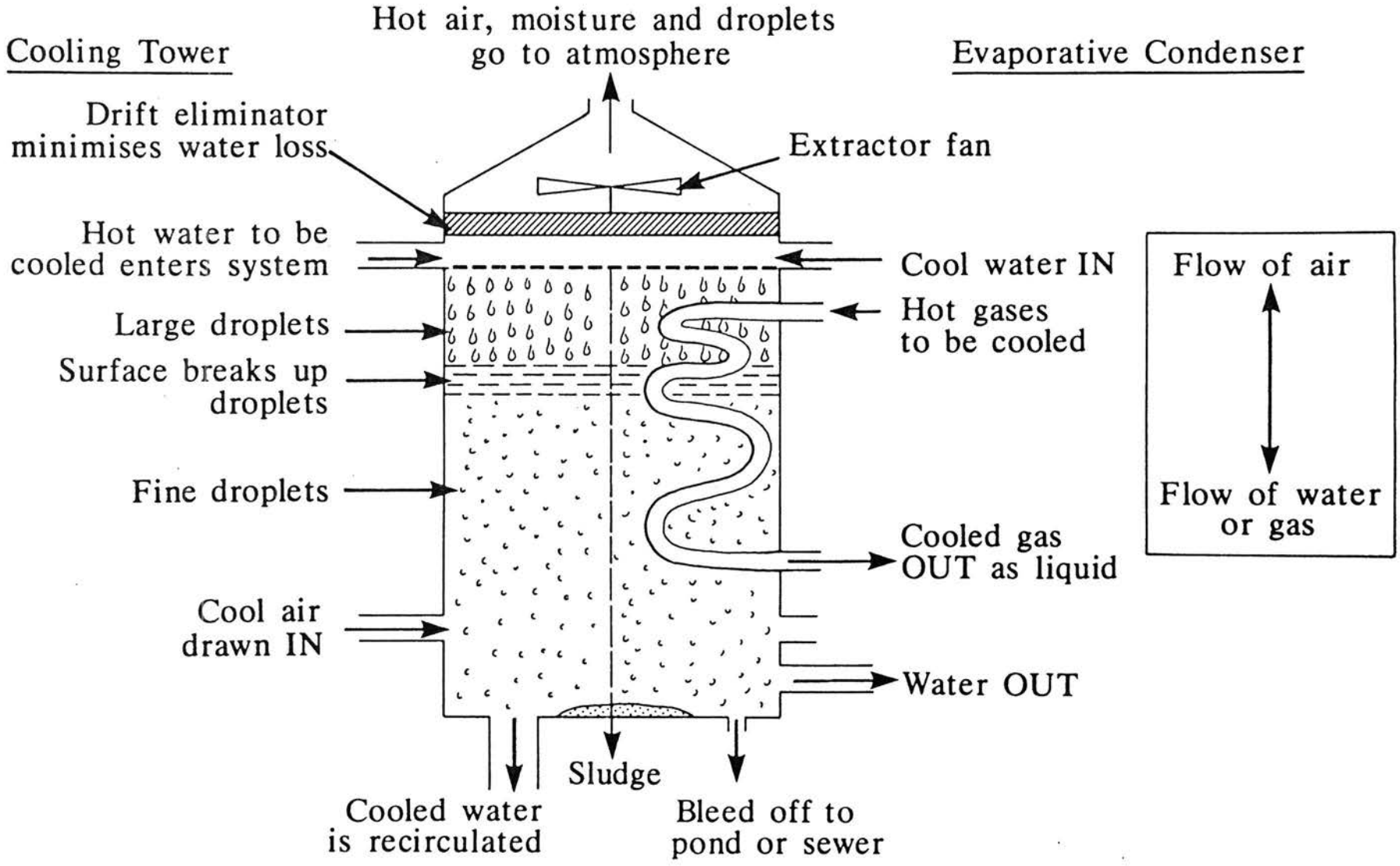


FIGURE 2.1

sharp decline in the number of organisms. In one tower, conductivity best predicted the level of culturable legionellae ($p<0.05$), but pH, water temperature and relative humidity, were also important ($p<0.15$). The level of viable organisms, as detected by staining techniques, was best predicted by relative humidity. They concluded that sampling of cooling towers at a single point in time has limited value, and that both cooling tower operating parameters and environmental factors influence growth.

In an early survey in Britain 18 cooling towers were sampled and one grew legionellae while eight probably had the organisms (Dennis et al, 1982). In the later and larger Public Health Laboratory Service survey legionellae were grown in cooling towers from 6 of 9 hotels tested, 5 of 13 hospitals and in 13 of 24 business premises. Overall, 52% of cooling towers grew legionellae (PHLS, 1985a). However, during the 1984 Dennistoun Outbreak in Glasgow only 4/142 (2.8%) towers tested grew legionellae (Jackson, 1985; Ad-hoc Committee 1986; Bhopal, 1986). In Vermont USA, where two outbreaks had occurred, a survey of 185 towers led to culture of legionellae from 18. Use of ground waters, low turbidity and high pH were associated with growth of legionellae (Witherell et al, 1984).

While natural draft cooling towers in power stations have legionellae the organisms are present in low concentrations (Bonnell and Rippon, 1985) and no such tower has been implicated in an outbreak.

Few outbreaks in Britain have been firmly linked to cooling towers (5 up to 1987 according to the Report of the Committee of Inquiry, 1987), but the size of such outbreaks tends to be large. Table 2.6 lists details of many of the major outbreaks associated with cooling towers and summarises the evidence of airborne transmission via this route.

The evidence for the causal link between cooling towers and Legionnaires' Disease is firm (Eickhoff, 1979; Fraser, 1980; Bartlett et al, 1986) but some remain sceptical. Muder and colleagues (1986) reviewed the evidence for airborne transmission and the role of cooling towers and concluded that,

"the widespread acceptance of cooling towers as an established disseminator for *L pneumophila* appears unwarranted".

Their argument that aspiration of organisms from the oro-pharynx was a principal mode of transmission was as follows: Legionnaires' Disease has a low attack rate which is typical of aspiration and not airborne transmission; the bacillus has pili which is a

TABLE 2.6

EVIDENCE IMPLICATING COOLING TOWERS AND EVAPORATIVE CONDENSERS AS SOURCES OF ORGANISMS LEGIONNAIRES' DISEASE OUTBREAKS

Date	Place	No cases& type of outbreak	Sero-group	Evidence of cooling tower involvement	Comment on evidence	Reference
1968 (July)	Pontiac, USA	144 Pontiac Fever in one building	I	1. Guinea pigs exposed to air and water aerosol from evaporative condensers succumbed. 2. L pneumophila demonstrated in guinea pig lung tissue. 3. Drift from evaporative condensers circulated by air conditioning.	Strong	Glick (1978)
1976 (July)	Philadel-phia, USA	182 Legionnaires' Disease associated with a hotel	I	1. Epidemiological evidence linked lobby and sidewalk of hotel to infection. 2. No other mode of transmission elucidated. 3. Numerous cooling towers in the building.	Weak	Fraser (1977)
1977/78	Blooming-ton, USA	39 Legionnaires' Disease: nosocomial and community-acquired	I	1. L pneumophila found in cooling tower but tower was non-operational for much of the time. 2. Exhaust from cooling tower shown to be drawn into stairway and elavator shaft.	Weak to Moderate	Politi (1979)
1978 (July)	Atlanta, USA	8 Legionnaires' Disease: hotel associated	I	1. L pneumophila isolated from evaporative conderser in golf club. 2. Air from evaporative condenser blew onto golf course where affected persons played. (30 metres away) 3. Risk of Legionnaires Disease varied with amount of golfing.	Moderate	Cordes (1980)

Date	Place	No cases& type of outbreak	Sero-group	Evidence of cooling tower involvement	Comment on evidence	Reference
1978 (Aug/ Sept)	Memphis, USA	44 Legionnaires' Disease: nosocomial	I	1. L pneumphila isolated from cooling tower in hospital 2. Use of (untreated) cooling tower closely associated in time with outbreak. 3. Spatial distribution of cases fitted with distribution of cooling tower exhaust (case-control study). 4. Air tracer studies showed drift could reach air intakes and street.	Strong	Dondero (1980)
1979 (June/ July)	Wisconsin, USA	13 Legionnaires' Disease: hotel associated	I	1. L pneumophila isolated from cooling tower on top of hotel. 2. Exhaust from cooling tower shown to enter meeting room (via chimney) where most cases had been. 3. Cooling tower treatment omitted prior to outbreak. 4. Outbreak terminated after chlorination of cooling tower and sealing of chimney.	Strong	Band (1981)
1980 Summer	Burling-ton USA	85 Legionnaires' Disease: nosocomial	I	1. L pneumophila, identical on monoclonal antibody subtyping to patient isolate, isolated from cooling tower 150 metres away from the cluster of cases in hospital. 2. Tower was upwind of cases. 3. Place of work or hospitalisation of cases associated with above tower. 4. Antibody titres in workers at this cooling tower higher than workers in control cooling tower.	Moderate to strong	Klaucke (1984)
1983 (Nov/ Dec)	Reading, UK	15 Legionnaires' Disease: Community-acquired	I	1. L pneumophila serogroup I isolated in three, and Legionella merissi isolated in one, of 10 cooling towers examined. 2. Cases all went to the city centre. 3. No other sources identified	Weak	Anderson (1985)

Date	Place	No cases& type of outbreak	Sero-group	Evidence of cooling tower involvement	Comment on evidence	Reference
1984 (June/ Sept)	Glasgow, UK	33 Legionnaires' Disease: Community-acquired	I	1. L pneumophila, identical to patient isolates, grown from one cooling tower, downwind of cases 2. All cases lived or worked near tower. 3. Geographical distribution of cases compatible with windborne spread of drift. 4. One, housebound patient lived 900 metres away.	Moderate/ Strong	Ad hoc Committee (1986)
1985 (April)	Stafford, UK	101 Legionnaires' Disease: nosocomial	I	1. L pneumophila identical to patient isolate isolated from the pond draining cooling tower. 2. Water from pond shown to be sucked into air-conditioning system (no airbreak). 3. Drift from tower drawn into air inlets and circulated to outpatient department.	Strong	Committee of Inquiry (1986)
1985 (Nov)	Glasgow	16 Legionnaires' Disease: nosocomial	I	1. L pneumophila, identical to patient isolates, grown from hospital cooling tower. 2. Drift shown to enter areas where patients beds were.	Strong	Timbury (1986)
1987 (April/ May)	Wollongong Australia	44 + Legionnaires' Disease: Community-acquired	I	1. All cases went to shopping mall 2. Cultures from a cooling tower in mall, and a local hospital, and those from patients were of same subtype. 3. Wind direction compatible with drift movement of 50 to 70 metres to air intakes.	Moderate (reassess when full report)	Christopher (1987)
1988 (April May)	London UK	70 + Legionnaires' Disease: Community-acquired	I	1. Identical L pneumophila from patient & cooling tower 2. Drift shown to enter areas where patients worked or travelled to. 3. Outbreak ceased when tower cleaned	Strong	PHLS (1988) and Dr CLR Bartlett (Lecture 1989)

characteristic of organisms which cause pneumonia by aspiration; ingestion of water was the only behavioural association shown to be statistically significant in the 1976 Philadelphia outbreak case-control study; oral inoculation of guinea-pigs can induce illness (Katz and Matus, 1984); and, instrumentation of the respiratory tract often precedes nosocomial legionella pneumonia. However, as the authors concede, legionellae rarely colonise the oropharynx (Bridge and Edelstein, 1983; Baumgardner et al, 1988). Their two principal arguments against airborne spread of Legionnaires' Disease (not Pontiac Fever) were: in outbreaks where cooling towers were incriminated (e.g. Memphis, 1978) other possible sources of infection were not tested or the results ignored when positive; and there has been a lack of prolonged and complete surveillance to unequivocally show that treatment of incriminated cooling towers led to the termination of outbreaks. Though few would agree with the extreme view of Muder and colleagues their review is important for it highlights that in most cases (particularly sporadic ones) the source and mode of transmission remain unexplained, that the role of cooling towers may have been over-emphasised and that non-airborne modes of transmission need study.

There are other fundamental questions which arise from acceptance that cooling towers are a source of infection. At what concentration do cooling towers emit

legionellae and is this sufficient to cause disease? The infective dose in humans is unknown (Committee of Inquiry, 1987) but lack of person-to-person spread suggests that it is not small. In guinea pigs inhalation of more than 2,400 organisms can induce lethal pneumonia (Baskerville et al, 1981) though about 130 organisms can cause an infection (Berendt et al, 1980). (In the latter study the lethal dose was much larger, in the order of 100,000 organisms). In monkeys one million organisms can induce a fever and microscopic lesions but not macroscopic changes of pneumonia (Baskerville et al, 1981). For healthy humans the infective dose is probably larger but for the immunocompromised it may be smaller.

Most aerosol sources produce concentrations of organisms in the order of 100,000 organisms per cubic metre (Bovallius et al, 1981; Tyndall et al, 1982a; Tyndall et al, 1985). Of interest, was the observation by Tyndall and colleagues (1985) that legionellae were grown from air around cooling towers only during cleansing procedures. They extrapolated experimental data on the infective dose in animals and estimated the dose to be 14 million organisms for humans. Based on their data on legionella concentrations around cooling towers (2-528 bacteria per 100 litres of air) they calculated that nine years of inhalation would be required to cause human disease (Tyndall et al, 1985).

This calculation indicates the fundamental gaps in our knowledge on transmission.

Assuming that cooling towers do emit sufficient organisms to cause infection, can organisms survive their airborne journey to the respiratory tract? The epidemiological evidence suggests that the aerosol drift travels and remains infective at distances of 150 metres (Klaucke et al, 1984), and perhaps 900 metres or more (Ad hoc Committee, 1986). Most pathogenic bacteria, but not those for which air is the natural habitat, lose their viability rapidly (seconds or minutes) in air (Bovallius et al, 1981). Even in air fully saturated with water, aerosols evaporate completely in less than a second leading to dessication of micro-organisms (Morrow, 1980). Legionellae are more sensitive to drying than other organisms such as *E Coli* (Katz and Hammel, 1987). How then do we explain our observations?

Laboratory data show that legionellae suspended in aerosol at 65 degrees relative humidity survive for at least two hours (Hambleton et al, 1983). (Broth grown organisms which were in the exponential phase of growth, survived less well than those grown on solid medium). Virulent sub-types were shown to survive better than non-virulent ones (Dennis and Lee, 1988). Plausibly, legionellae are also hardy in air in natural conditions. The observation by Berendt (1981) that aerosol

suspensions with an algal extract survived better than those containing tyrosine saline suggests that natural aerosols may be hardier than those created in the laboratory. However, algal extract did not increase the virulence of such aerosols to guinea pigs. Tyndall and Domingue (1982b) made the same observation. While cooling tower drift has yielded cultures of legionellae at close range (Neill et al, 1985) cultures have not been made at a distance.

Droplets exceeding 100 microns settle rapidly to the ground but smaller ones (droplet nuclei) can be suspended in air, held there as a discrete "pocket", and travel in air currents, by diffusion and by sedimentation and be carried long distances (Bovallius et al, 1981). Turbulence of air and the temperature inversion layer shorten the journey and encourage deposition (Cox, 1987). Though the events between the formation of aerosol and its inhalation remain unclear the knowledge we have is compatible with airborne spread from cooling towers.

Other infections have been shown to have occurred after the carriage of organisms over long distances including psittacosis, Q fever and anthrax (Bovallius et al 1981; Cox, 1987). Tuberculosis, smallpox and measles are other diseases associated with airborne spread over moderate distances (Langmuir, 1980). These precedents

add credibility to the view that cooling tower drift can travel a moderate distance and still cause infection.

The ecological relationship between legionellae and higher unicellular organisms has been emphasised (Fliermans, 1984; Spriggs, 1987). Barbaree and colleagues (1986) found protozoa in water from a cooling tower linked to an outbreak and demonstrated intracellular multiplication of organisms. Possibly, the survival of legionellae in air may be enhanced by their carriage within amoebae or protozoa. Such a particle would be approximately 10-30 microns in diameter, too large to be inhaled into the bronchioles and alveoli where the pathogenic process is thought to commence (Morrow, 1980). However, dessication in air would occur and markedly reduce the particle size (Cox, 1987). On entry to the respiratory tract rehydration would occur. Whether such a particle could cause infection is a moot point.

Domestic Water Systems

Though domestic cold water systems have not been linked to infection (Bartlett, 1984, Bartlett et al, 1986) organisms are probably present in low concentrations within them and may seed hot water systems and cooling towers (Colbourne et al, 1986; Colbourne et al, 1988a). Bartlett (1984) comments that it would be

surprising if domestic water systems at all sites were not sources of infection.

Hot water systems consist of a source of fresh water, a water heater (calorifier), plumbing to distribute the hot water and a means of exit for the water (taps, showers). We might expect hot water systems to be free of legionellae as water does not recirculate and the water heater should raise the temperature of water to a level where legionellae would be rapidly killed. This is not the case. Legionellae can be grown from a high proportion of hot water systems. In the PHLS survey, the water systems of 55 of 104 hotels, 28 of 40 hospitals and 13 of 17 business premises (overall 60%) grew legionellae, usually in the hot water system (PHLS, 1985a). From Lower Saxony in Germany, similar results have been reported; organisms were grown from 70% of hospitals and 18% of hotels (Habicht and Muller, 1988). Even when the calorifier heats water to 60°c or more, legionellae can be grown and organisms are probably protected in "dead legs" and sludge where heat does not penetrate well.

Muder (1986) and colleagues comment that prior to 1982 most outbreaks were associated with cooling towers, but subsequently mostly with hot water systems. They argue that conclusions were often reached on weak evidence. Indeed, Garbe and colleagues' (1985)

description of an outbreak initially blamed on the domestic water system and later traced to a cooling tower emphasises the need to avoid hasty conclusions. Nevertheless, as the masterly reviews by Bartlett and colleagues show (1984a, 1986), hot water systems are undoubtedly an important source of transmission of disease. Of 21 clusters in England and Wales investigated to the period to 1986, nine were associated with domestic hot water systems mainly in hospitals and hotels (Committee of Inquiry, 1987). There were no cooling towers at most of these sites (PHLS, 1985b)

In 1980 two patients who had renal transplants developed Legionnaires' Disease. Both had occupied the same single room. *L pneumophila* of serogroup 6 was isolated from the patients and the shower unit in the room, but not from other environmental sources (Tobin et al, 1980). Later, a cluster of cases occurred in a hotel. *L pneumophila* serogroup I was recovered from the hotel's water system but from no other source (Tobin et al 1981). Following these initial observations many investigations traced infection to hot water systems. One illustrative study was that of an outbreak in a hotel in Benidorm, Spain (Bartlett et al, 1984b). This hotel was also associated with the Scottish cases in 1973 (Grist et al, 1979). Fifty nine cases of pneumonia were diagnosed in 1980 among guests, of whom 25 had laboratory evidence of Legionnaires' Disease. The hotel's water

supply was supplemented by pumped well water until a pump failure occurred. The first case occurred one week after re-connection of this supplementary supply. Also, water from the refrigeration unit's cooling water circuit was re-directed to the main cold water tank and recirculated. Epidemiological data showed that guests who bathed or showered first were most at risk. It transpired that Legionnaires' Disease had occurred in this hotel throughout the period 1971 to 1980 but after continuous chlorination was started and the water temperature raised, cases ceased. Another case occurred in 1988 due to a lapse in control measures (Dr C L R Bartlett, lecture, 1989). The authors proposed that the well water seeded organisms into the domestic water supply which multiplied in the refrigeration unit's water circuit and the peripheral plumbing. People were possibly infected as they used the water for bathing (Bartlett et al, 1984b; Bartlett et al, 1986).

Several other outbreaks have ceased after treatment of domestic water supplies (Fisher-Hoch et al, 1981; Shands et al, 1985). The experience of Helms and colleagues (1983) is noteworthy. They reported 24 cases of nosocomial pneumonia in a hospital where the hot water systems were widely contaminated with legionellae. After great difficulty in eradicating the organism from the environment they resorted to continuous hyperchlorination and succeeded in both achieving

suppression of the outbreak and consistently negative water samples. However four sporadic cases occurred over five years. The costs of continuous chlorination were high and the water distribution sysem was damaged (Helms et al, 1988).

The epidemiological data suggests that infection follows the inhalation of contaminated aerosol generated as water is ejected from the taps or shower head. Guinea-pigs exposed to aerosols from potable water surces have become ill (Meenhorst et al, 1983). Hanrahan and colleagues (1987) found that cases were more likely than controls to occupy areas close to shower facilities and *L pneumophila* grown from the ward showers was identical to an organism grown from a patient. By contrast, in a study in Iowa, USA, cases spent less time showering than controls (Helms, et al, 1983). These authors suggested that attention should turn to water taps. Farr and colleagues reported failure of a no showering policy in preventing nosocomial Legionnaires' Disease (1988). Meenhorst and colleagues (1985) found that 12 of 21 nosocomial cases had not showered and four others who were strictly confined to bed during hospitalisation had their beds close to the taps. In a hospital-acquired outbreak, which was eventually linked to a cooling tower, there was no association between risk of infection and proximity to taps and showers (Garbe et al, 1985).

Again, major gaps in knowledge about transmission exist. Studies around showers have shown that only small amounts of *L pneumophila* are aerosolised and then, the concentrations are higher when the shower is turned on and rapidly decline (Dennis et al, 1984; Bollin et al, 1985 b; Woo et al, 1986). Dennis and colleagues (1984) calculated that a man would need to breathe air near such sources for 227 minutes to inhale one bacterial cell. Though legionellae can be isolated from showers alone this does not prove showers to be a source of infection (Muder et al, 1986). One report on the concentrations of legionellae around taps showed these to be low but the aerosol particle size was small enough to enter the lower respiratory tract (Bollin et al, 1985b).

Aerosol can also be formed in natural waters by the bubble jet drop mechanism (when bubbles formed underwater and collapse at the surface of the water) and when air flows over water. Organisms are concentrated on the surface of bubbles and the air water interface (Baxter, 1985) and in biofilm (Colbourne et al, 1987 and 1988b). Virulent organisms may be more hydrophobic and hence more likely to be concentrated.

While the airborne route remains the favoured hypothesis linking hot water systems to infection, the role of aspiration cannot be discounted (Johnson et al, 1985; Bartlett, 1984; Muder et al, 1986; Brennen et al,

1987) and especially needs to be borne in mind for post-surgical patients (Johnson et al, 1985; Woo et al, 1986). Katz and Matus were able to induce a febrile, self-limiting illness among guinea-pigs which were given water containing legionellae, and guinea-pigs which had legionellae inoculated into the gastroinstinal tract by gastric intubation (1984). Pneumonitis, splenitis and seroconversion were demonstrated.

Whirlpools and spas

Whirlpools and spas have recirculating warm water (in which chlorine may be rapidly depleted due to organic contamination) and agitation of water which produces aerosol; an ideal ecology for the dissemination of legionellae. Data on the prevalence of legionellae in such systems in Britain were not found. In the Netherlands 11 of 28 whirlpools with free chlorine levels of less than 0.3 milligrams per litre harboured legionellae compared with 0/23 of those with higher chlorine levels (Groothius et al, 1985a).

Several Pontiac Fever outbreaks have been linked to whirlpools and spas (Mangione et al, 1982; Spitalny et al, 1984). The largest outbreak of Pontiac Fever in Britain occurred in Scotland in 1988 and has been linked to a whirlpool (Goldberg et al, 1988) but in their report the authors fail to mention that there was a cooling tower at the premises (personal observation). One

outbreak of Legionnaires' Disease associated with a whirlpool spa has also occurred in Britain (PHLS, 1985). Legionnaires' Disease has been reported at a natural hot spring spa in France (Bornstein et al, 1989). A wide range of species or subgroups of legionellae were cultured from spa water which was rich in minerals and had a temperature of 39 to 45 degrees centigrade.

The theoretical importance of this source is that the airborne mode of transmission has been clarified. Mangione and colleagues (1982) showed that the whirlpool aerator produced water droplets small enough (2 to 8 microns) to penetrate the tracheobronchial tree and that the risk of infection was related to time spent in the whirlpool.

Other sources

Any source of aerosolised water is a potential source of infection but though legionellae have been demonstrated to be present in many waters they have not always been shown to have caused infection (Bartlett et al, 1986; 151). For example, Oppenheim and colleagues (1987) found legionellae in water samples taken from dental stations and demonstrated that dental drills generate aerosols but found no cases of disease. Apparently, no outbreaks have been associated with cold water aerosols.

Bacterial contamination of nebulisers is common (Barnes et al, 1987) and Legionnaires' Disease probably occurs by this route (Arnow et al 1982; Jones et al, 1984). Five patients in a Chicago hospital developed Legionnaires' Disease and had used nebulisers (Arnow et al, 1982). Though the link was not conclusive (the organisms were also found in tap water and subtyping was not done) the inference was clear: use sterilised water in nebulisers. One possible case in Scotland was apparantly infected in this way (Fallon R J, personal communication).

The water in room humidifiers yields legionellae and may be a source of infection (Bartlett, et al 1986). Kaan and colleagues (1985) reported a patient with Legionnaires' Disease who was exposed to aerosol from a mechanical humidifier but the hot water system of the hospital also contained legionellae. Jones and colleagues (1984) grew legionellae from room humidifiers while Woo and colleagues (1986) demonstrated experimentaly that room portable humidifiers generated aerosols containing legionellae especially when filled with water from the hot water tank.

Industrial coolant fluid composed of a water and oil mixture and contaminated by *L. Feelei* caused an outbreak of Pontiac Fever (Herwaldt et al, 1984). Interestingly,

the pH of the oil water mixture was 8.5 to 9.5 at which legionellae grow comparatively poorly.

Clearly, vigilance is required whenever humans are exposed to aerosolised, warm water but the major sources of infection are hot water systems and cooling towers.

iii Subtyping: linking disease to source of infection

Legionella organisms are ubiquitous yet the disease is rare. As 80-90% of infections are due to *L pneumophila* of serogroup 1 (Reingold et al, 1984; Woodhead et al, 1986b) which is also a common serogroup found in environmental samples, the isolation of organisms from a cooling tower or a calorifier is weak evidence that the source of disease had been traced even if the serogroup is the same. When both patients and environmental isolates are available the organisms can be compared using one of several techniques (Edelstein et al, 1986 Stout et al, 1988; and see section 1 e).

If an environmental isolate matches the clinical isolate this is strong (but not conclusive) evidence that the source of infection was the source of that isolate. These methods have been applied in the investigation of several outbreaks.

Subtyping studies have shown that the strains commonly found from environmental sources are not those

causing human disease. Watkins and colleagues (1985) found that the OLDA subgroup was predominant in water collected from buildings unassociated with infection. In contrast, the Pontiac subgroup predominated in buildings associated with Legionnaires' Disease and this subgroup caused 44 of 50 cases of Legionnaires' Disease they investigated. Of 300 environmental isolates studied by Brindle and colleagues (1987), only 13% belonged to the Pontiac subgroup of serogroup 1 and 22% were of OLDA subgroup. By contrast, 85% of 41 clinical isolates from sporadic cases of Legionnaires' Disease were part of the Pontiac subgroup and only 5% were of the OLDA subgroup. Dournon and colleagues (1988) made similar observations in Paris; 94% of clinical isolates, but only 35% of environmental isolates, had the antigen 2 marker (MAb 2 marker). All the outbreak related cases had this marker. Seven of the eight cases infected by organisms without the MAb 2 marker were immuno-compromised. They concluded that the MAb 2 marker indicates agent virulence. Stout and colleagues made similar observations (1988). Bollin and colleagues observed that legionellae isolated from a hospital where clinical infection had occurred were more virulent to guinea-pigs that those isolated from a hospital where no disease had been observed. These observations help explain why disease may not arise even when legionellae are present.

Joly and Winn (1984) categorised 25 isolates as epidemic related and then analysed the antigenic characteristics of the legionellae using monoclonal antibodies. They found three patterns, A, B and C. Fourteen of fifteen clinical isolates from patients involved in epidemics were pattern A while eight of nine isolates from sporadic, nosocomial cases were pattern B. A community-acquired case had pattern C. Cooling tower water isolates yielded legionellae with pattern A and potable water isolates had pattern B. They concluded that different sources harbour different subtypes of legionellae and that type of infection i.e. sporadic versus epidemic, may depend on the nature of the source of infection.

The reason why certain subtypes are more virulent remains unknown. Nor do we know what determines the dominance, within an environment, of one type over another. But the observation that chlorination can change the colonising subtypes seems important (Edelstein et al, 1986; Stout et al, 1988)

Evidence is emerging that the antigenic markers detected by monoclonal antibodies may be unstable and altered by heat and other stimuli (Colbourne J, lecture to the 4th European Working group on Legionella Infection, July 1989). If so, the value of this method

of linking environmental and human isolates is diminished.

PART 3 PRINCIPLES OF PREVENTION OF LEGIONNAIRES' DISEASE

Knowledge on prevention has been derived from first principles and observational studies, and only rarely by experiment. Hence, this section is written as a summary of current guidelines which are largely based on understanding of the ecology and epidemiology of the disease.

Prevention and control measures may be directed at the host, agent or the environment but, to date, the control of the environment, particularly to minimise dissemination of organisms, has been emphasised.

(a) Host

Few of the classical infectious disease control measures directed at the host apply. Person-to-person spread does not occur so isolation of cases is unnecessary. Antibiotic cover for at-risk groups during an outbreak has not been systematically studied but in view of the low attack rate the benefits would be difficult to demonstrate particularly in a community setting. After an outbreak in a transplantation unit, and pending treatment of the water supply, oral erythromycin was given to 24 immunosuppressed patients. No case of infection occurred. Among nine

immunosuppressed patients who did not receive erythromycin, 5 cases occurred (Vereerstraeten et al, 1986). Antibiotic cover may have a role under such circumstances.

Though vaccine development is technically feasible (Wong et al, 1979) the rarity of the disease probably renders its development unlikely and, arguably, unnecessary.

Behavioural change may be important. Assuming that cigarette smoking is truly part of the causal chain for Legionnaires' Disease and that the relative risk is two or more as suggested by most studies (Storch et al, 1979; England et al, 1981) then a reduction in incidence of about one-third would be predicted in future non-smoking communities (appendix Part 1). However, the means by which smoking increases host susceptibility is unclear and this remains a theoretical issue.

Two practices which could help prevent nosocomial infection are the nursing of susceptible patients (particularly the immunocompromised) away from sources of aerosol (showers, taps, open windows) and the flushing of taps and showers by staff prior to their use by patients (Bartlett et al, 1984b; Meenhorst et al, 1985; Bollin et al, 1985b; Woo et al, 1986).

(b) Agent

Presently neither the attenuation of the virulence of legionellae nor their eradication is possible. No intermittent method of control can permanently eradicate the organism from a water system, possibly because the inflow of water seeds the system (Colbourne et al, 1988a) and even continuous treatment may allow legionellae to grow (Ribeiro et al, 1987; Timbury et al, 1988). With the possible exception of environments where immuno-suppressed patients are nursed (Edlestein, 1983; Seidler, 1984) no attempt should be made to either seek or attempt to eradicate legionellae unless disease has occurred; there is a consensus on this principle (Fraser, 1984; Jacubowski, 1984; Harper, 1986; Department of Health and Social Security, 1989). The aim is to manipulate the environment to minimise the growth and dissemination of legionellae. However, there is evidence that there is pressure from commerce and industry for both testing and attempts to eradicate (Industrial Water Society, 1985; Committee of Inquiry, 1987).

(c) Environment

The principal sources of infection (see Part 2, e, ii) are cooling towers, hot water plumbing systems whirlpool spas, nebulisers and similar apparatus. The principles of prevention are:

Buildings and their fittings should be designed and built to minimise the opportunities for the growth and transmission of legionellae;

administrative control of monitoring should be clear and effective;

general hygiene and maintenance checks should be done on a regular basis;

and, disinfection should occur.

Bacteriological testing is not important. Official recommendations have been based on these principles (Department of Health and Social Security, 1980; Committee of Inquiry 1986 and 1987; Health and Safety Executive, 1987; Department of Health and Social Security, 1988). The recommendations are based on experience, observational research and common sense and only occasionally on scientific experiment. Recommendations have also been made by others and widely published (Industrial Water Society, 1985; Chartered Institute of Building Service Engineers, 1987). The recommendations differ for cooling towers and hot water systems.

i Cooling towers

The structure, mechanism and function of cooling towers has been discussed in Section 2 e, part ii.

The replacement of evaporative cooling towers by air cooling systems has been advocated to reduce the risk of

Legionnaires' Disease (Committee of Inquiry, 1986) but such a change is likely to be costly, slow and incomplete except for new hospitals (Department of Health and Social Security, 1987b and 1988). Better design, particularly of drift eliminators, may make replacement unnecessary (Wigley, 1987; Oughton, 1987; Deal, 1987). Presently, the risk of Legionnaires' Disease needs to be minimised. There is no agreed safe threshold for legionellae so maintenance needs to be as good as possible with due regard to the costs. Fortunately, controlling legionella growth helps maintain the function of towers.

Ideally, buildings with cooling towers should be sited distant to and downwind of densely populated areas, ventilation ducts and windows should not draw fresh air contaminated by cooling tower drift, and building should be designed to allow easy access to cooling towers and their components (Deal, 1987; Oughton, 1987; Department of Health and Social Security 1988;). As Oughton (1987) points out winds and local air currents are unpredictable and the direction of drift movement is not controllable.

Towers made of porous materials such as wood have been more frequently associated with outbreaks (Mallison, 1980) and these should be avoided. Internal fittings should also be non-porous. Certain types of rubber washers and other components encourage the growth of legionellae and should be avoided (Colbourne et al 1984)

and those which inhibit growth used e.g. thiuram containing rubbers (Niedeveld et al, 1986).

Bacterial replication is enhanced in stagnant water so dead-legs (pipes where there is no free flow of water) should be avoided. Dead-legs may prevent the complete drainage of the system and allow rapid re-seeding by legionellae following treatment. The plumbing of the cooling tower should be independent and where piping is shared, for example, at the point of drainage, an air-break should functionally separate the two plumbing systems (Mallison, 1980; Department of Health and Social Security, 1985).

The cooling tower drift, normally about 0.1% of the water flow in new towers but much higher in old ones (Miller, 1979), is the vector of infection and its quantity should be minimised. Effective drift eliminators need to be fitted and routinely checked (Wigley, 1987). However, drift eliminators may not entrap aerosol particles as small as 5 microns (Oughton, 1987). Drift can by-pass the drift eliminator by leaking through cracks in the body of the tower. This danger is less in induced draught towers where a fan ejects air, hence creating a partial vacuum which draws in fresh air, than in forced draught towers where the fan blows air into the tower, when drift may be forced out of

cracks and faults in the body of the tower (Department of Health and Social Security, 1988).

Several outbreaks have followed a period of shut-down of a tower and evidently legionellae multiply in these circumstances. When shutdown is unavoidable the tower should be drained and treated chemically prior to re-use (Harper, 1984).

The water source should be from the mains whenever possible (Bartlett et al, 1986: 146) as other sources are more likely to be contaminated with or support growth of legionellae. The pH, hardness of the water and the total dissolved solids influence the growth of legionellae and these should be monitored to ensure that the least favourable conditions are maintained (Department of Health, 1989). Chlorination becomes less effective at alkaline pH (Department of Health and Social Security, 1989) but chlorine is less rapidly dispersed (States et al, 1987).

Though the design, structure, site and water source of cooling towers are probably of fundamental importance in control, often little can be done for existing towers. Hence, the strong emphasis on the need for hygiene. The longstanding guideline that towers be serviced at least annually but preferably bi-annually has been supported by the PHLS survey which found that *legionella* isolates were

less common in towers serviced twice a year or more (PHLS, 1985a). The aim is to check for and repair damage, remove organic and inorganic fouling and to disinfect and hence to inhibit legionella growth. Disinfectants need not be specific to legionellae and bacteriological testing is unnecessary. Many biocides have been shown to be effective in vitro (Department of Health, 1989) but, excepting chlorine, the evidence for their efficacy in the field is scant (Hollis and Smalley, 1980; Domingue et al 1989; Department of Health and Social Security, 1989). Foaming, which may be associated with the use of chemicals, should be avoided as legionellae can be concentrated a thousandfold or more in foam (Colbourne et al, 1987).

Experience from several outbreaks shows that cooling tower maintenance is often overlooked and vigilance is essential. Responsibility for maintenance and monitoring should be given to named persons who undergo appropriate training, and records of maintenance should be kept (Department of Health and Social Security, 1988).

There is no proof that the above measures will eliminate the risk of infection from cooling towers but infection from properly mantained towers has not been reported. Studies on the costs versus benefits of the above procedures have not yet been done. The widespread use of biocides may have hazards and their effects, in

the long term, on the environment and humans remain unknown (Oliver, 1986; Department of Health and Social Security, 1989).

Whether the above recommendations have been widely implemented remains unknown though two borough councils in Britain have developed questionnaires to identify at-risk systems (Penn, 1986). Anecdotes abound about the poor quality of maintenance of cooling towers indicating that some cooling towers are neglected.

ii Domestic water systems and other sources

As for cooling towers, guidelines on the control of legionellae in domestic water systems derive from knowledge of the ecology of the organisms together with observations on the circumstances of outbreaks (Harper, 1984 and 1986; Department of Health and Social Security, 1980, 1988; Department of Health, 1989).

Access to water tanks, plumbing and the calorifier is important and is clearly the responsibility of the architect and builder. Thorough cleansing and chlorination is required prior to commissioning a new building or a new water system (Harper, 1984). Stagnation of water is to be avoided (as is the use of stagnant source waters), hence dead-legs should be minimised. Legionellae can survive in stagnant tap water for more than a year (Schofield, 1985a). Cold

water tanks should be fitted with secure covers which prevents the ingress of debris and dust.

The temperature at which water is held is probably the most important factor. Cold water should be maintained at 20 degrees centigrade or less, while hot water should be stored at 60 degrees centigrade or more and delivered to the taps at 50 degrees centigrade or more (Plouffe et al, 1983b; Department of Health and Social Security, 1988) Where children, the elderly and the mentally handicapped are at risk of scalding, the tap water temperature should be about 43 degrees centigrade (Department of Health and Social Security, 1980; Bainbridge and Black, 1988). Maintaining hot water at these temperatures is expensive, and continous chlorination is both expensive and damaging to pipework (Helms, et al 1988), and hence, the report that ultraviolet light inhibited the growth of legionellae on hospital wards is encouraging (Farr et al, 1988). Intermittent heating is another means of control (Plouffe et al, 1983b).

Routine maintenance on a yearly basis with cleaning followed by chlorination is recommended. Calorifiers not in use should be drained and chlorinated before re-use.

While gas and steam heated calorifiers do not grow legionellae, electrically heated ones do (Canada Diseases Weekly Report, 1984) as the sludge below the electrical element is not thoroughly heated and protects organisms. Sludge accumulation can be minimised by having a concave rather than convex base to a calorifier (Department of Health and Social Security, 1988). Temperature statification can also prevent even and thorough heating but is reduced by placing calorifiers horizontally rather than vertically. Plumbing fixtures and fittings should be made of approved materials which do not promote the growth of legionellae (Colbourne et al, 1984) though, in practice, the benefits may not be clear (Ribeiro et al, 1987)

As with cooling towers eradication of legionellae is not possible, so the goal of treatment programmes is to contain the multiplication of the organisms in a water supply. This seems sufficient to prevent outbreaks (Best et al, 1983; Jacubowski et al, 1984; Groothuis et al, 1985b; Ribeiro et al, 1987; Helms et al, 1988).

No action is presently advocated for the water systems of private homes even though legionellae may be present (Arnow and Weil, 1984; Redd and Cohen, 1987).

Clearly, biocides cannot be used for water which may be drunk and chlorine is the recommended disinfectant.

As legionellae grow in cold water with a chlorine level of less than 0.5 ppm, ideally, chlorine levels should be maintained at 1 to 2 parts per million (Harper, 1986)

For the primary prevention of infection from other sources i.e. whirlpool, spas, nebulisers etc,. similar principles of good design and hygiene apply (Bartlett et al, 1986).

RESEARCH ISSUES ARISING FROM THE LITERATURE REVIEW

Since 1977 much has been learnt about Legionnaires' Disease ,yet, such is the complexity of the ecology of legionellae, that many fundamental questions about agent virulence, sources of infection, mode of transmission, infective dose, host susceptibility, and disease prevention have been only partially answered. Further, most of the insight on these matters derives from the study of outbreaks. The source of infection, mode of transmission, and means of prevention (among other matters) in the case of sporadic (or non-outbreak) infection remain uncertain.

Epidemiological research on Legionnaires' Disease, particularly comparison of disease frequency over time and between places, has been hindered by the lack of a universally used definition, the varying presentation and severity of the disease, the absence of pathognomonic clinical signs, the lack of a fully satisfactory diagnostic test (particularly in regard to sensitivity), the rapid changes in the diagnostic tests, and differences in both medical and disease surveillance services.

Nonetheless, epidemiological studies have made a major contribution in identifying sources of infection generally, and in the context of outbreak investigation.

However the full potential of epidemiology has not been realised, partly for the reasons given above and partly because though many associations have been noted, generally, they have not been explained. For example, geographical variation in disease frequency offers a means of studying the environmental determinants of the disease on a community basis. Though often observed, such variations have not been studied in depth.

Of the gaps in knowledge identified in the literature review this research was conducted to fill two in particular. First, to develop an approach for measuring geographical variation, for assessing whether observed variation is artefact, and if not, for studying other explanations, particularly environmental ones. Second, by undertaking appropriate studies as above, to improve understanding about the source of non-outbreak infection.

The next chapter describes the framework within which the research was conducted.

CHAPTER 3

OUTLINE OF THE RESEARCH AIMS, QUESTIONS, OBJECTIVES, DESIGN AND PLAN

OUTLINE OF THE RESEARCH AIMS, QUESTIONS, OBJECTIVES, DESIGN AND PLAN

Aims

The principal aims were to describe the spatial distribution of Legionnaires' Disease in Scotland, particularly for non-outbreak, locally-acquired cases, and to develop and test hypotheses to explain observed variations. The underlying aim was to advance understanding of the source of locally-acquired, non-outbreak infection.

Research questions

Among the research questions to be addressed were the following:

What was the incidence of Legionnaires' Disease in Scotland and was it higher than in other comparable countries?

Was there variation in incidence of the disease within Scotland by health board, city or postcode-sector of residence? If so, did the variation persist when outbreak and travel-associated cases were excluded? Did travel-associated cases also show variation in incidence?

Was the variation an artefact due to errors in ascertainment of cases or differentials in the

ability and tendency to make the diagnosis? From observations on variation what might be inferred about the likely sources of the non-outbreak disease?

Were cooling tower maintenance programmes such that there was a risk of infection from them?

Was there a relationship between living or working near to a cooling tower and the risk of non-outbreak Legionnaires' Disease? Did the relationship apply to travel-related infection?

Were there outbreaks of infection which were missed by the surveillance system?

Key hypotheses

Among the many hypotheses arising from the above questions were the following which were central to the thesis that non-outbreak Legionnaires' Disease in Scotland was acquired from cooling towers.

1. Geographical variation in Legionnaires' Disease exists and is neither a result of differential rates of testing and other similar causes of artefact, nor of differences in host susceptibility.
2. Spatial variations in travel-associated cases will be dissimilar to those of locally-acquired cases.

3. For both outbreak and 'sporadic' cases there will be a spatial association between the numbers and location of cooling towers and the risk of Legionnaires' Disease in a locality.
4. During the time period concerned the maintenance of cooling towers was not such that the risk of Legionnaires' Disease was minimal.

Objectives

The main objectives to be met, in order to answer the research questions and achieve the aims of the study were these:

1. To prepare a case-list of probable and possible cases of Legionnaires' Disease in Scotland to the end of 1986 and to categorise them as travel and non-travel related.
2. To estimate the incidence of Legionnaires' Disease for Scotland, each Health Board, selected cities and within areas of some cities.
3. To prepare point pattern maps by place of residence, (and when possible by place of work) for the cases of Legionnaires' Disease.
4. To ascertain the number, location and maintenance procedures of cooling towers.
5. To measure the relationship between the place of residence of cases (and if possible place of work) and the location of cooling towers.

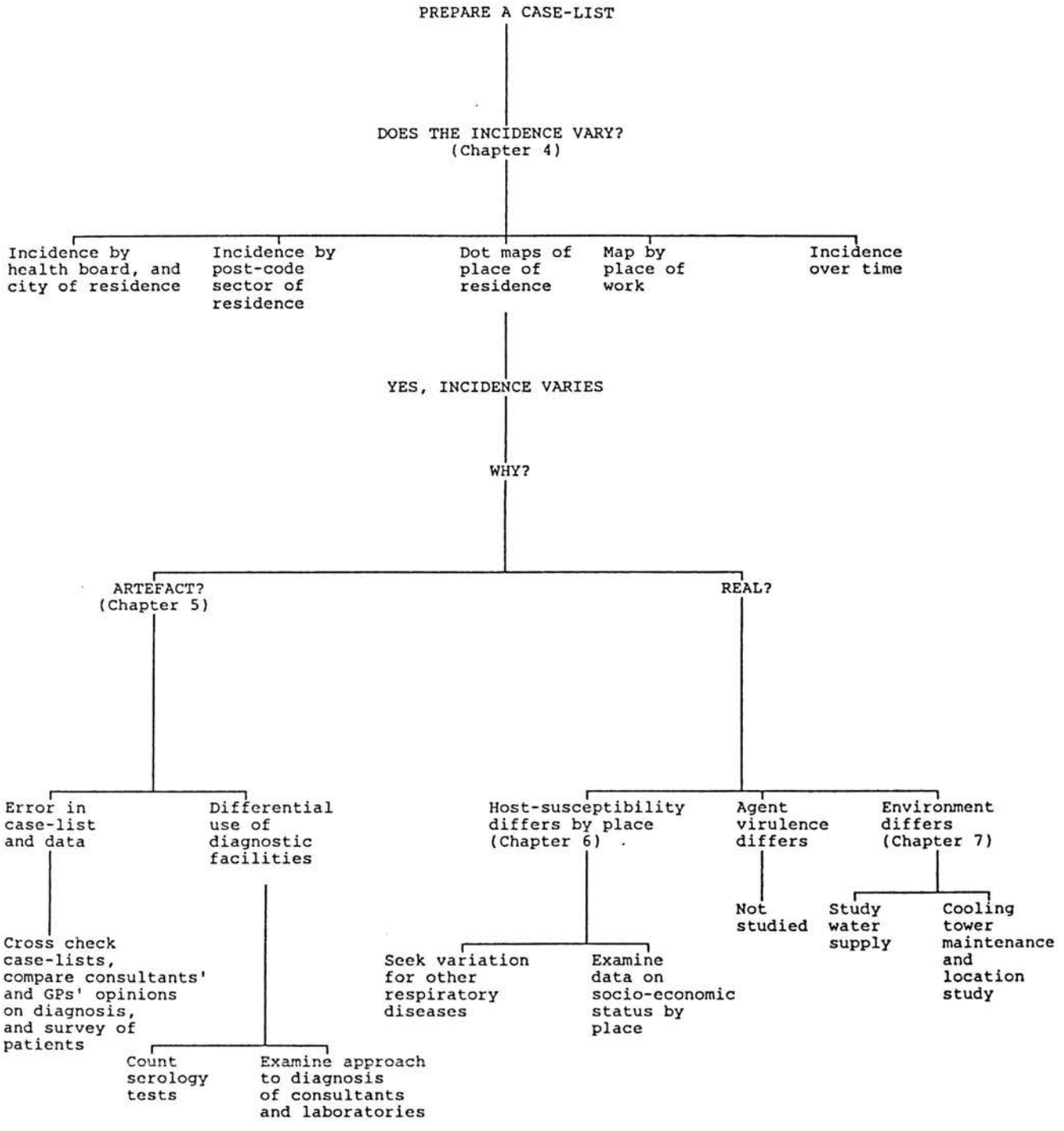
6. To estimate the numbers of serology tests done for Legionnaires' Disease by geographical area and selected hospitals, and relate this to the number of cases of pneumonia and Legionnaires' Disease; the ratios being an indicator of the likelihood of a patient with pneumonia being tested for Legionnaires' Disease.
7. To assess whether the spatial variations observed for Legionnaires' Disease are specific to this disease or also found in other respiratory diseases (and hence are a reflection of variation in host susceptibility or availability and use of services).
8. To assess whether differences in the socio-economic characteristics of populations, as a possible indicator of host susceptibility, might explain the varying incidence of Legionnaires' Disease.

The design and research plan

All studies were retrospective because Legionnaires' Disease is relatively rare and its incidence fluctuates from year-to-year. A prospective study with sufficient numbers of cases to answer the research questions was not practical. Figure 3.I shows the framework within which studies were planned. The key question was, did the incidence vary and if so why? Variation might be an artefact resulting from an incomplete and erroneous case-list, or differential use of diagnostic facilities. Alternatively, the variation may be real and due to

FIGURE 3.1

PLAN OF STUDIES UNDERTAKEN



either host factors or to environmental factors. The possibility that the agent might vary in virulence was not tested but clearly offers an important alternative explanation.

CHAPTER 4

EPIDEMIOLOGICAL STUDIES WITH SPECIAL REFERENCE TO GEOGRAPHICAL VARIATION

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INTRODUCTION

Disease surveillance is based on the study of the epidemiology of diseases and has as its aim the detection of changes in disease patterns to allow the curtailment of epidemics and to help understand the causes, transmission and natural progression of disease.

The absence of variation in the frequency of disease by time, place and person suggests uniform susceptibility and uniform exposure to the causative agent. By contrast, variation indicates that either the explanation lies in genetic heterogeneity or environmental differences (Rose, 1987). If the latter, the disease is potentially preventable. Fluctuations in disease incidence over time, especially short periods, argues against genetic heterogeneity as a cause of spatial variation. Data on variation can also help set local priorities and direct efforts at disease curtailment.

Legionnaires' Disease is an environmentally-acquired bacterial pneumonia so its incidence would be expected to vary with the degree of environmental exposure to the source of organisms. If no variation existed then it could be concluded that the population's exposure to the pathogen was uniform. Several outbreaks have shown that the degree of risk is related to the degree of exposure to a source. However, the source of exposure for

sporadic cases, which account for some two-thirds of cases is obscure (Bartlett et al, 1986).

Though the largest outbreaks of disease have been linked to cooling towers the commonest known source of infection in Britain is domestic hot water systems (Bartlett et al 1984 and 1986; Committee of Inquiry, 1987). If this also applies to sporadic disease then people could be infected from one of thousands, perhaps millions of aerosol sources at home, at work, and other public buildings. The degree of risk in a community would relate to the qualities of the water (including maintenance procedures) and to the opportunity of exposure to high risk buildings such as hospitals or hotels. Any pattern observed in the geographical distribution of cases would reflect the water supply and the risk of exposure to high risk buildings. Variation in incidence over time could occur in two ways: natural alterations in water quality which altered the ecological relationship between legionellae and their water environment and alterations in the type of hot-water systems used in a community. Temporal fluctuations for non-outbreak infection would probably be gradual rather than abrupt.

If however, the principal source of infection for sporadic disease was cooling towers then those people who work, live or travel in their vicinity would be at

greatest risk. The pattern of distribution of cases would bear a relationship to that of the location of cooling towers. In these circumstances temporal fluctuations would not only be related to change in the quality of water and to alteration in the number and use of cooling towers but also to the quality of maintainance of cooling towers. Abrupt temporal fluctuations would be more likely.

Let us assume that non-outbreak, non-travel cases were exposed to infection within their homes. Then the organisms could come from the domestic water supply (Stout et al, 1987) or from an external aerosol source entering through air-intakes (Bhopal and Fallon, 1988). If the domestic hot water system was the vector of infection then any variation in the distribution of cases by place of residence should reflect either local variation in the quality of the water or differences in the presence of sources of aerosol within homes e.g. showers. Given a common water supply, one would predict that the spatial distribution of cases would be uniform or there would be somewhat more disease among those with more aerosol sources in the home. If, however, the infection were acquired within the home but as a result of aerosol entering from outwith, the pattern of residence of cases would be expected to bear a relationship to that of the putative source of aerosol i.e. cooling towers.

In both instances, the place of residence (or workplace) of travel-associated cases would be expected to be independent of the location of cooling towers or other postulated sources of infection. The same would apply to hospital-acquired cases, but since such patients are likely to live or work near to the hospital in which they are admitted, the place of residence or workplace might show clustering around the hospital.

Lastly, if the assumption is correct that the contaminated aerosols cause no other pneumonia except for Legionnaires' Disease, then any clustering observed should be specific to Legionnaires' Disease.

The aim of the study described in this chapter was to give an account of the epidemiology of Legionnaires Disease in Scotland for the period to 1986, in terms of person, time and place (but particularly the latter) and to explore some of the points discussed above.

The specific objectives were to:

1. Prepare a case-list and categorise patients by travel history, and as outbreak, nosocomial or sporadic cases.
2. Describe the incidence of Legionnaires Disease over time.
3. Describe the age and sex distribution of cases.

4. Seek geographical variation in the incidence of disease by Health Board, local authority district, city and at a small-area level.
5. Answer the following specific questions:
   (a) were outbreaks missed by the routine surveillance system?
   (b) was the G31 district associated with a high incidence of Legionnaires' Disease prior to the 1984 outbreak?
   (c) Did the high incidence of disease in the G31 district cease after the 1984 outbreak was controlled?

METHODS

a. Sources of Data

The Department of Laboratory Medicine, Ruchill Hospital, Glasgow has been acting as the reference laboratory for Legionnaires' Disease for Scotland. Testing for Legionnaires' Disease started in 1977 using the indirect immunofluorescence antibody test based on formalin-killed antigen prepared by the Centres for Disease Control, Atlanta, USA. In February 1978 a heat-killed antigen was prepared and the indirect immunofluorescence antibody testing was done with this local antigen and the Centres for Disease Control antigen. Since 1978 a pan anti-human immunoglobulin has been used which detects both IgG and IgM in the patients' serum. As new Legionella species and subtypes were detected new heat-killed antigens were prepared; by November 1978 a polyvalent antigen to *L. pneumophila* serogroups 1-4 was in use. It has been the normal practice of the laboratory to maintain quality control by cross-checking a sample of sera using antigen prepared at either the Centres for Disease Control or the Public Health Laboratory Service, Colindale, England. Culture of the organism has been offered since February 1978. The culture medium mainly used was BCYE (buffered charcoal yeast extract). Direct fluorescence antibody testing has been done since February 1978. The records of this laboratory were the starting point of the study.

A case-list of Legionnaires' Disease cases diagnosed in the laboratory has been maintained manually and laboratory forms relating to all requests for legionella tests stored in chronological order. (Unfortunately, the 1980 forms had been lost). Index cards hold laboratory details of positive cases up to December 1984 after which these details are on a microcomputer. In addition, for many cases diagnosed after mid-1984, further details have been sent by consultants in response to a questionnaire (henceforth called consultants' forms) from the laboratory. The case-list at the laboratory notes, for most patients, the name, age, sex, principal laboratory findings, onset, type of illness, and country of illness. Some of these data were based on telephone discussions with hospital staff by the laboratory consultant, Dr. Fallon. Address was not noted.

The Communicable Diseases (Scotland) Unit, also at Ruchill Hospital, receives returns from Scottish laboratories (including Ruchill Hospital) on a voluntary basis and from these has prepared lists of cases of Legionnaires' Disease. Again, address was not noted. Copies of the laboratory request forms of many patients are also archived.

These two lists were cross-checked to form a master list of possible Legionnaires' Disease cases. (The lists were not, by any means, identical). The

laboratory forms for these patients were then studied to obtain missing identification, clinical, and laboratory test details. Most patients with non-*L. pneumophila* infections were excluded at this stage in view of the difficulty in interpreting the significance of laboratory results as none were culture positive (Taylor, 1987).

Table 4.1 lists the variables on which data were sought. Verification of the diagnosis and the post-code were the major requirements. The primary source of information was the laboratory form but these were usually incomplete (see Appendix 2 for details); rarely, even the source of the sample could not be identified. The six-stage procedure to obtain missing addresses and hence postcodes and other information was as follows:

(1) When the hospital of admission was not known the requesting laboratory was contacted for further details.

(2) The hospital medical records officers were asked, in writing, for missing addresses, consultants' names, and general practitioners' names, and addresses.

(3) When this failed, the lists held on microfiche at the Information Services Division (Edinburgh) of pneumonia patients admitted to Scottish Hospitals were scanned for a match and when successful data obtained on postcode and hospital number.

TABLE 4.1

DATA SOUGHT FOR EACH CASE

Name
Age
Sex
Address and postcode
Name of hospital and hospital number
Name of consultant in charge
Name and address of general practitioner
Date of onset
Travel history
Evidence of nosocomial or outbreak related infection
Clinical history, particularly for evidence for pneumonia
Laboratory results with dates of submission of samples

(4) The homonyms of the names of the remaining patients were then matched against the computerised named listings of pneumonia admissions (held at the Information Services Division of the Common Services Agency) and a printout of matched names examined. Data on postcode and hospital number were found for about 25 patients.

(5) For the remaining patients, the microbiology laboratories who sent the original specimens were contacted and requested to help in completing patient details.

(6) Completion of missing information by consultants and general practitioners (see below).

When known, both the consultant in charge of the acute episode and the general practitioner were sent a letter and a computer printout with the name, address, date of birth, hospital number and date of onset. The consultants were asked to state their view on the validity of the diagnosis. General practitioners were asked the same question and also for information on the patient's occupation, history of travel abroad and history of hospitalisation prior to illness. Both consultants and general practitioners were asked to complete missing data fields and to correct errors in the computer printout. The data file was altered as

appropriate. A comparison of the author's views on the diagnosis based on laboratory held information and those of general practitioners and consultants was made (see chapter 5, where the extent of agreement is discussed). When lack of clinical information was an obstacle to the classification of patients as cases, the clinicians were contacted by telephone.

General practitioners and consultants were also asked for permission to write to patients. A further check on address, date of onset and travel history and other relevant details was made for those patients where permission was granted and who replied to a postal questionnaire. (The methods of this study and results are discussed in Chapter 5). Again, the data file was corrected.

Hence, the final data set was based on data from Ruchill Hospital laboratory and the Communicable Diseases Scotland Unit on all cases, feedback from general practitioners or consultants or laboratories in most cases, data from the Information Services Division in some cases and, from patients in some cases. The case-definition was now applied.

b. Case definition for Legionnaires' Disease

The cases were assigned to three groups as below:

(i) Probable diagnosis. This was defined as a case with a clinical history of an acute pneumonia or acute lower respiratory tract infection and one or more of the following:

(1) Culture of the organism.

(2) For *L. pneumophila* only

(a) A four-fold rise (or fall) in titre to at least 64 but no other clinical diagnosis.

(b) A static titre of 256 or more but no other clinical diagnosis.

(c) Positive direct fluorescence antibody test on respiratory secretions or tissue using specific reagents.

(d) Legionella antigen detected in urine.

For two cases exceptions were made for the sake of consistency: both had static titres of less than 256 but were categorised as cases during the 1984 Dennistoun outbreak (Ad-hoc Committee, 1986).

(ii) Possible diagnosis. This was defined as;

(1) A case with an unclear clinical history but laboratory results compatible with infection.

(2) Static titre of 256 or four-fold rise in titre to 64 or more for species other than L pneumophila.

(3) A static titre of 64 or 128 with a history of

acute pneumonia or lower respiratory tract infection with supporting epidemiological evidence e.g. an outbreak.

(4) A case meeting the criteria under (i) above but with evidence of another cause of pneumonia in addition to Legionnaires' Disease.

(iii) Unlikely or unclear diagnosis. This was defined as a case with;

(1) A clinical history of pneumonia, no other diagnosis and a titre of 32 or less.

(2) Clinical history unclear but a titre of 64 or 128

(3) A patient who was not acutely ill, irrespective of laboratory results.

c. Cross-reactions: Assignation of serogroup

Where antibody titres were raised to more than one serogroup the assumption was made that this was a cross-reaction, not dual infection, and the following approach was taken. The causative serogroup was said to be the one to which there was a four-fold rise in titre or the one with the higher titre (by two dilutions). Where this did not resolve the problem the assignation was on empirical grounds e.g. serogroup I was assigned rather than other serogroups because it is the commonest cause of infection and also, the sensitivity and specificity of

the serological tests for *L. pneumophila* serogroup I have been documented.

d. Interpreting serology titres

Where serology titres were borderline, the result least likely to support the diagnosis was recorded e.g. if the first serum was 64/128 and the second serum 128/256 this was recorded as 64 and 128, not as 64 and 256.

e. Handling missing data fields

The mapping package described below excludes patients with missing data in relevant fields. In a study of geographical variation the exclusion of cases due to missing data could lead to serious bias as it is plausible that data may be more likely to be missing for cases from one region than another. The following approach was taken to minimise missing data fields:

Age Two patients were assigned the median age for the whole group (56 years)

Months of Onset For 19 cases the month of onset was deduced from the date of submission of the laboratory test. The onset was arbitrarily said to be two weeks prior to the first laboratory request.

Clinical Illness Where no data was obtained, the patient was assigned to the "unlikely or unclear diagnosis" category.

Travel History The infection was coded as locally-acquired unless there was evidence to the contrary.

Postcode See below.

f. Geographical data: preparation for analysis

With a few exceptions (described below), coding the health board and city of residence was based on the full address at the time of illness of the patient. The addresses were manually converted to 7-unit postcodes using the postcode directories of the General Post Office. All post-codes including those derived from medical records were double-checked as errors were found to be common. The post-codes, together with age and sex, were the basis of the calculation of standardised legionella morbidity rates for the production of the chloropleth maps.

The postcodes were converted to 10 digit national grid reference numbers using GRIDREF, a computer program (Nimmo et al, 1984) (this was done by the Operational Research Unit at Aberdeen). The point-pattern maps were prepared using the grid reference numbers.

Where the address was missing but the post-code was found, for example in those cases where information came from the Information Services Division, the city and health board were indirectly derived. For patients

where neither the address nor postcode was obtained, the health board of hospitalisation was used as an indicator of the health board of residence (data to show that the margin of error was low is in appendix 3 and has been published (Bhopal, 1989).

g. Analysis of data and preparation of maps

Numerical data were coded by the writer and punched by the staff of the computer laboratory onto the Amdahl mainframe computer of the University of Newcastle upon Tyne. They were transferred to an IBM PS2/30 microcomputer. The data were held on Dbase III files for ease of editing and manipulation (Ashton-Tate, 1985). The statistical Package for the Social Sciences (SPSS PC) was used for statistical analysis (Norusis, 1986). Most analyses used standard statistical tests such as the chi-squared test and the Mann-Whitney Test (Siegel, 1956; Norusis 1986).

Figures (except maps) were prepared in the Excel spreadsheet and graphics package (Microsoft Corporation, 1987). Geographical analysis of incidence rates in Scotland, towns and cities and the health districts of Greater Glasgow Health Board (which is reported in Chapter 6, table 6.4) were done manually using census data for the denominator. All other geographical analysis and mapping were done using LINEMAP, a package of programmes for mapping with microcomputers which has

been developed by the Northern Health Boards' Operational Research Unit, Aberdeen (Nimmo et al, 1984; Nimmo, 1989; Northern Health Boards Operational Research Unit). Based on the postcode, age and sex,standardised incidence rates and standardised morbidity ratios, can be automatically calculated for each health board, local authority and postcode sector in Scotland. The output of the programme is as follows:

the actual and expected number of cases;

the crude rate;

the incidence rate standardised to the local population;

the standardised morbidity ratio (observed divided by expected, based on standardised rates);

the statistical significance level (derived from the Poisson distribution) i.e. the probability that the observed incidence was not statistically different from the expected incidence;

and the significance level adjusted for multiple comparisons.

The statistical details are given in appendix 2. The analysis of incidence by local authority is not reported in this thesis except briefly in Chapter 7, Results section b), because the findings were similar to those arising from the analysis by health board, and towns and cities. Chloropleth maps of age and sex standardised incidence rates by health board or postcode sector were prepared from the rates calculated as above. In

In addition probability maps were made using the statistical significance levels. Lastly, using the grid reference number point-pattern maps were made.

In the point-pattern maps where several points have the same grid reference number (each residential postcode pertains to a cluster of addresses housing about 100 people) the width of the symbol denoting a case is proportionate to the number of cases e.g. where a circle of 2 mm diameter is used to denote one case, a circle of 4 mm would be drawn for two cases. Maps were prepared to show cases in the areas adjacent to the areas of interest e.g. maps are of Greater Glasgow Health Board and surroundings.

In accord with the study objectives and hypotheses the principal cases of interest were those without a travel history, who were not involved in an outbreak and who were not nosocomial. Essentially, if these cases were sporadic their spatial distribution would be expected to be random. The geographical distribution, by place of residence, of the travel-related infected group was used for comparison.

Age and sex standardised to rates by health board, local authority district and post-code sector were calculated for the above group using the LINEMAP (SMRATE routine) programme with 1981 census data and the

appropriate population group (as indicated in the results section). The statistical significance level for a rate in a geographical unit was derived by the computer programme, from the Poisson distribution as is the recommended and widely used procedure (Boots and Getis, 1988).

This mapping package served the requirements of this study well but it had several technical limitations. Firstly, each map had to be prepared individually, not in batches, and the process took about one hour and a quarter (preparation and printing) and, for ease of photocopying, maps were made in black and white and coloured by hand. Secondly, once prepared no modifications were possible. Thirdly, only one data file could be used at one time to prepare maps. Fourthly, the postcode sector boundaries were only approximately correct and the symbol in point-pattern maps was not plotted exactly within the appropriate postcode sector boundary.

The maps of Greater Glasgow Health Board and the City of Glasgow show the River Clyde as a blue line. For point-pattern maps location of residence of cases is shown as a red circle, location of workplace as a green diamond and location of cooling towers (Ch7) as a blue square.

Where two separate sets of data required comparison (e.g. the maps in chapter 7) a transparency was prepared, superimposed and photocopied. The size of the maps could not be exactly controlled as the printing programme maximises the amount of space available. Hence some maps were slightly larger than others, even though prepared in the same manner. Lastly, postcode sector details were not entered onto maps as the disease patterns were then obscured. However, transparencies of the Greater Glasgow Health Board area and the City of Edinburgh showing the location of key postcode sectors, the direction North, approximate location of the general hospitals and some other general information are provided in the back binding cover, and can be overlaid on the maps.

RESULTS

a. Categorisation of cases and laboratory basis for the diagnosis

There were 456 potential cases of whom 378 were categorised as probable cases (83%) and who will now be referred to as cases, 54 (12%) as possible cases of whom six were patients with evidence of dual infection, and 24 (5%) categorised as unlikely or unclear. Details of laboratory and other data on non-cases are given in appendix 5.

All except one of the cases had a clinical history of either acute pneumonia (the great majority) or a lower respiratory tract infection. The exception had a "flu-like" illness but had been included on epidemiological grounds as a case in the 1984 outbreak. The laboratory evidence for the diagnosis in the 378 cases is summarised in table 4.2.

Two thirds had either a four-fold rise in titre (234) or a four-fold decline (16), and most of the remainder a static titre of 256 or more. Twenty cases had a static titre of less than 256 but 18 of them were either culture positive or DFA positive. Two patients who had static titres of 64 were included, for consistency, as they were part of the 1984 Dennistoun outbreak.

TABLE 4.2

LABORATORY BASIS FOR THE DIAGNOSIS FOR 378 CASES

Highest titre recorded	Culture positive	DFA positive	Antigen positive	Serology only	Row Totals
1. Four-fold rise in titre group (N=234)					
≤ 8	2	2			2*
32	1	1			2
64	1		1	14	16
128	5	1	1	42	49
256	6			65	71
512	4			72	76
1024				11	11
≥2048				7	7
2. Four-fold fall in titre group (N=16)					
≤ 64				2	
256				5	
512				6	
1024				2	
≥2048				1	
3. Static titre group (N=128)					
≤ 8	6	6			10*
16	2	1			2**
32	1	1			2
64	1			2+	3
128	1	2			3
256	2	1		49	51**
512				49	49
≥1024				8	8
Column Totals	31	15	2	332	378

* 2 patients were both culture and DFA positive
** 1 patient was both culture and DFA positive
+ These two patients were defined as cases in the 1984 outbreak in Dennistoun

Of the cases, 111 (29%) had travelled abroad during the incubation period. Of the others, 33 were associated with the Dennistoun Outbreak and 13 with the Glasgow Royal Infirmary outbreak (of the 16 cases reported by Timbury et al, 1986, three did not meet the present study criteria for inclusion as cases). Evidence of hospital exposure was found for another 16 cases (see appendix 6). There were 205 non-travel, community-acquired, non-outbreak cases. This was the group of greatest interest for the geographical analyses, particularly in comparison with the travel-related cases.

b. Serogroups

The serogoups are shown in table 4.3; serogroup I accounted for more than 90% of cases in both travel (93%) and non-travel (91%) groups.

c. Frequency of disease in time: annual and seasonal variation

Table 4.4 shows the number of cases and incidence rates per million by year of illness and travel history. (The 12 cases before 1978 were diagnosed retrospectively by analysis of stored serum). Figure 4.1 shows these data in graphic form for the years 1978 to 1986. The 9-year cumulative incidence rate for 1978 to 1986 was 71 per million and the mean annual incidence was 7.9. The annual incidence fluctuated markedly, particularly for non-travel cases which ranged from 1.6 per million in

TABLE 4.3

SEROGROUP BY HISTORY OF TRAVEL ABROAD

Serogroup	All	No Travel	Travel
1	346	244	103
2	8	7	1
3	8	4	4
4	7	5	2
5	2	1	1
6	1	1	-
8	2	2	-
9	1	1	-
14	1	1	-
Not known	1	1	
TOTAL	378	267	111

TABLE 4.4

NUMBER OF CASES (INCIDENCE RATE PER MILLION) BY YEAR AND TRAVEL HISTORY FOR ALL AND NON-OUTBREAK CASES

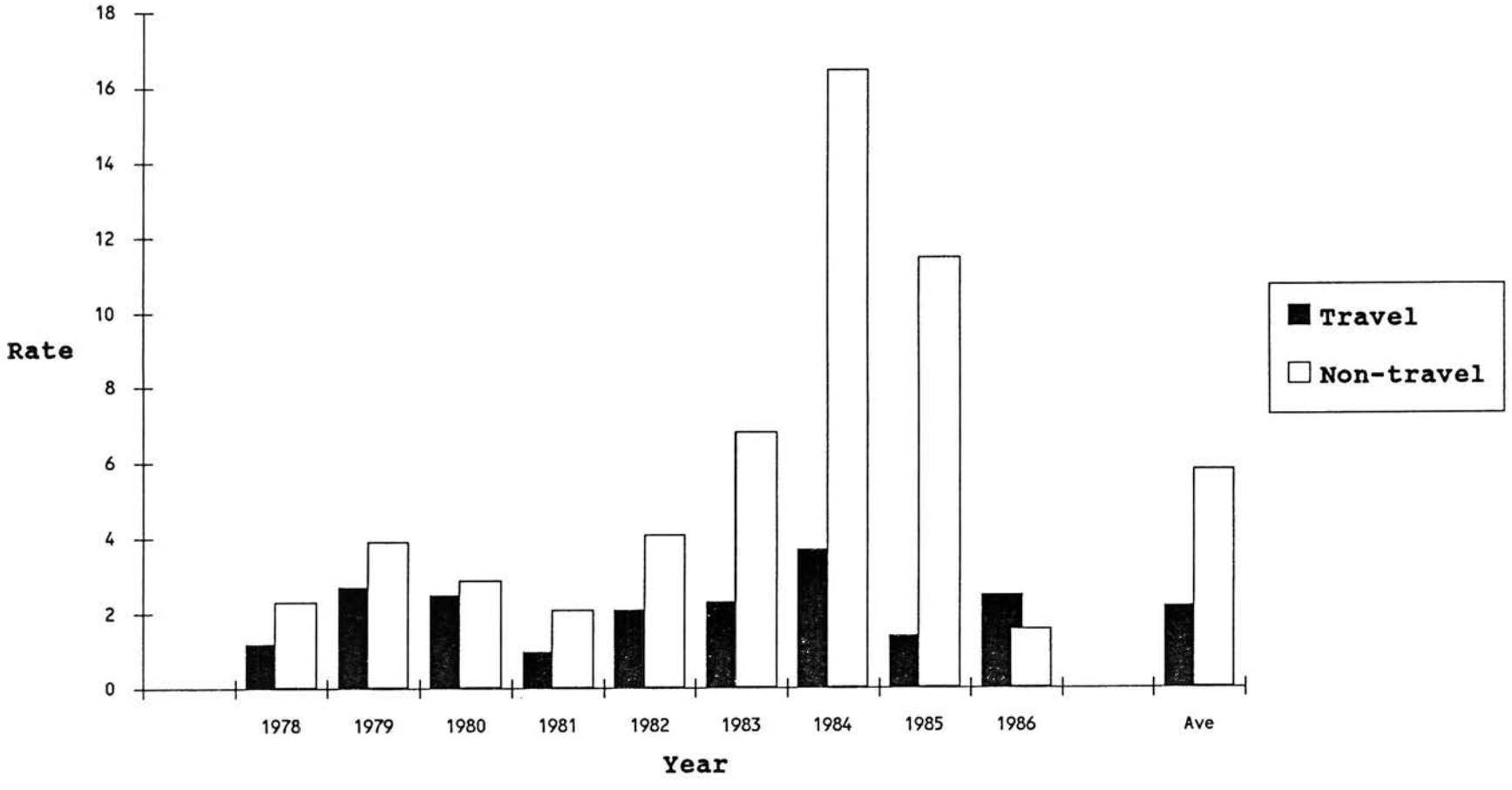
Year	No travel history				Travel History		All cases	
	All cases		Non-outbreak					
1973	0		0		4		4	
1974	1		1		1		2	
1975	0		0		0		0	
1976	0		0		2		2	
1977	0		0		4		4	
1978	12	(2.3)	12	(2.3)	6	(1.2)	18	(3.5)
1979	20	(3.9)	20	(3.9)	14	(2.7)	34	(6.6)
1980	15	(2.9)	15	(2.9)	13	(2.5)	28	(5.4)
1981	11	(2.1)	11	(2.1)	5	(1.0)	16	(3.1)
1982	21	(4.1)	21	(4.1)	11	(2.1)	32	(6.2)
1983	35	(6.8)	35	(6.8)	12	(2.3)	47	(9.1)
1984	85	(16.5)	52	(10.1)	19	(3.7)	104	(20.2)
1985	59	(11.5)	46	(8.9)	7	(1.4)	66	(12.8)
1986+	8	(1.6)	8	(1.6)	13	(2.5)	21	(4.1)
TOTAL**	267	(5.8)	221	(4.8)	111	(2.2)	378	(7.9)

* Due to the small numbers rates were not calculated for the years to 1977

\+ using 1985 population figures

** rates for totals are based on the average of 1978 to 1986 using the 1981 census data as denominator.

Figure 4.1 Incidence rate of Legionnaires' Disease (per million) by travel history.



1986 to 16.5 per million in 1984, a ten-fold variation. After excluding outbreak related infection there was still a 6-fold annual variation. The year-to-year variation is not a result of varying numbers of tests done (see data in table 5.7 and figure 5.1 in chapter 5) e.g. in 1986 the number of serological tests done at the acting reference laboratory was 3410 compared with an average of 3286 for the 3-year period 1983 to 1985. The annual incidence for travel-related infection varied less and the range was 1 to 3.7 per million (mean = 2.2).

The month of onset of illness (1978-1986 cases) is shown in figure 4.2, by travel and by outbreak history. While most travel-related cases were ill in summer and autumn, most non-travel cases were ill in autumn and early winter; a pattern which persisted when outbreak and nosocomial infections were excluded from the analysis (data not shown).

d. Frequency of disease by person: gender, age and travel history

Seventy one percent (268) of the cases were men and 29% (110) were women. Their ages ranged from 14 to 86 years and the mean was 59. Table 4.5 shows the cumulative incidence rate for 1978-1986 for men and women in five-year age bands and shows that the highest incidence was in the age-group 50 to 65 and that the excess in men occurred at most ages. There was no

Figure 4.2 Seasonal variation in Legionnaires' Disease by travel history

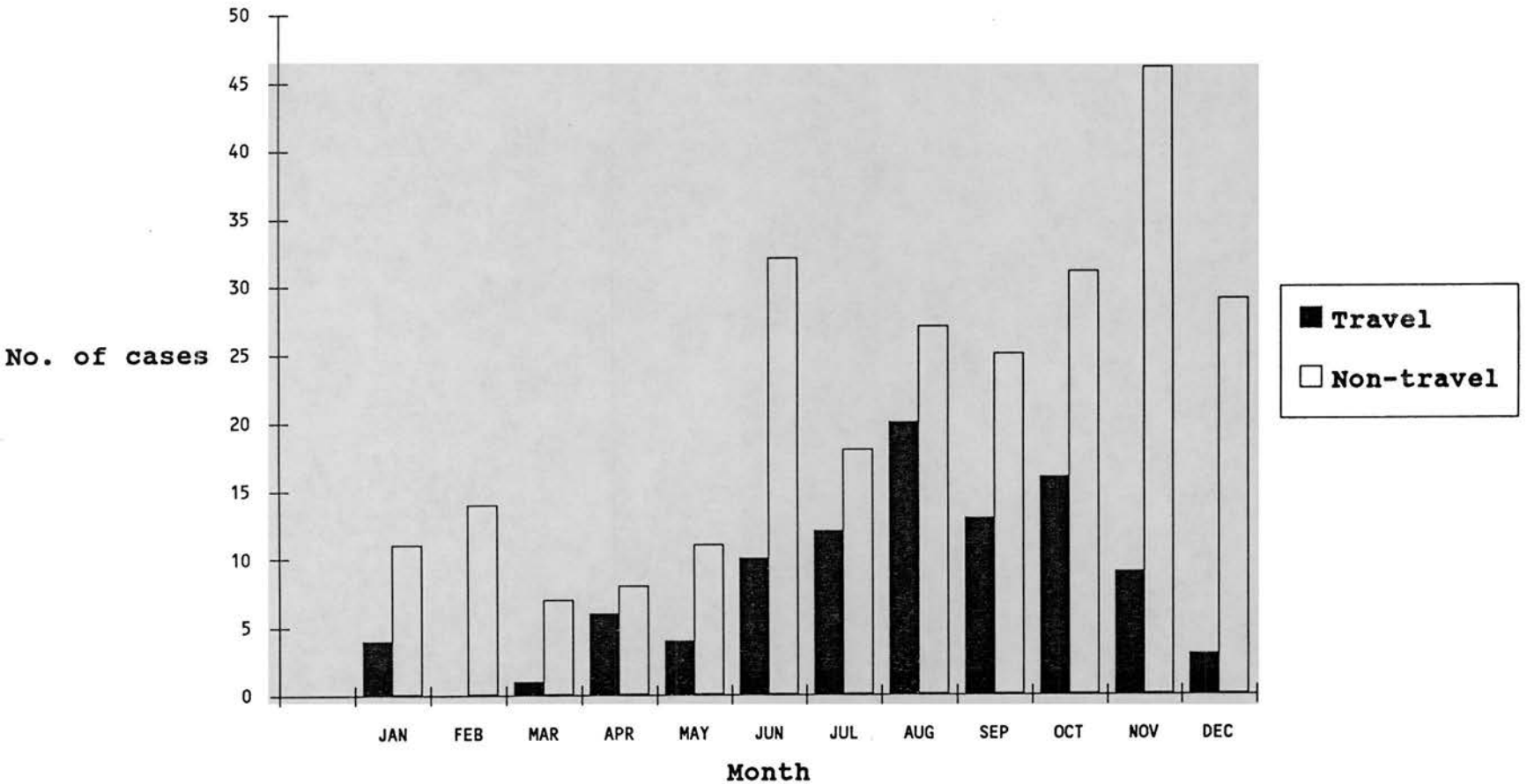


TABLE 4.5

NUMBERS OF CASES AND CUMULATIVE INCIDENCE RATE (PER MILLION) BY AGE AND SEX (1978-1986)

	Number of cases		Cumulative Incidence rate per million population	
Age group	Males	Females	Males	Females
10-14	1	0	4	0
15-19	1	0	4	0
20-24	1	1	5	5
25-29	9	3	51	17
30-34	7	0	38	0
35-39	12	2	79	13
40-44	14	5	97	33
45-49	31	6	218	40
50-54	34	17	239	111
55-59	42	20	298	130
60-64	54	21	463	151
65-69	22	11	204	80
70-74	15	8	177	65
75-79	13	6	251	64
80-84	3	3	131	53
85+	3	1	281	28
TOTAL/AVERAGE	262	104	105	39

substantial difference in the age-distribution of travel related and non-travel infection (data not shown).

Twenty nine percent of all cases, and 27% of cases diagnosed after 1977, gave a travel-history during the incubation period but this proportion varied annually as shown in table 4.6. However, this variation was largely dependent on the numbers of non-travel cases. Eleven of 12 cases recognised prior to 1977 were travel-associated. As for non-travel and outbreak cases, 1984 was the peak year for travel-related infection. Notably, in 1986 travel-related cases exceeded locally-acquired ones.

e. Frequency of disease by place of residence

Analysis was done for 1978 to 1986 cases, excluding two patients who were visitors and did not have a local address. For six patients (1.6%) the postcode was not obtained, but the hospital of admission or source of the request form was known. Could this information be used to deduce the probable health board of residence? Data in appendix 4 show that the health board of the hospital or general practice from which the laboratory request came correctly predicted the health board of residence in 89% of cases. As the margin of error was small, the health board of residence for six Scottish patients whose postcode was missing was assigned on the basis of source of laboratory request. Analysis by health board was for

TABLE 4.6

PROPORTION OF CASES WITH A TRAVEL-HISTORY BY YEAR

Year	Number of Cases	% of all Cases
1973	4	100
1974	1	50
1976	2	100
1977	4	100
1978	6	29
1979	14	42
1980	13	45
1981	5	31
1982	11	34
1983	12	24
1984	19	18
1985	7	11
1986	13	65
TOTAL	111	29

364 cases (excluding 2 English visitors), but for other analysis the six cases with missing postcodes were excluded (n=358). (See appendix 7 for information on the Health Boards).

(i) Health Board

Figure 4.3 and table 4.7 show that all health boards except Shetland had at least one case. The Greater Glasgow, Lothian and Lanarkshire Health Boards accounted for 75% of all cases, and 84% of non-travel cases (56% of travel-related cases) but had approximately 45% of the population. The age and sex standardised 9-year incidence rate varied markedly. The wide range in incidence rates and the extreme position of Greater Glasgow Health Board was particularly noticeable in the non-travel group (figure 4.3). Excluding the Shetland Health Board the non-travel associated incidence rate ranged from 5.6 (Highland) to 160.6 Greater Glasgow; a 29-fold variation. The range was 4.5 (Grampian) to 34.4 (Greater Glasgow) in the travel group; about an eight-fold variation.

The high rates in Greater Glasgow were not solely a result of outbreaks or nosocomial cases as table 4.8 shows; for non-travel, non-outbreak, community-acquired cases the rates were still three times the Scottish average and more than twice those in any other health

Figure 4.3 Incidence rate of Legionnaires' Disease (per million) by health board and travel history

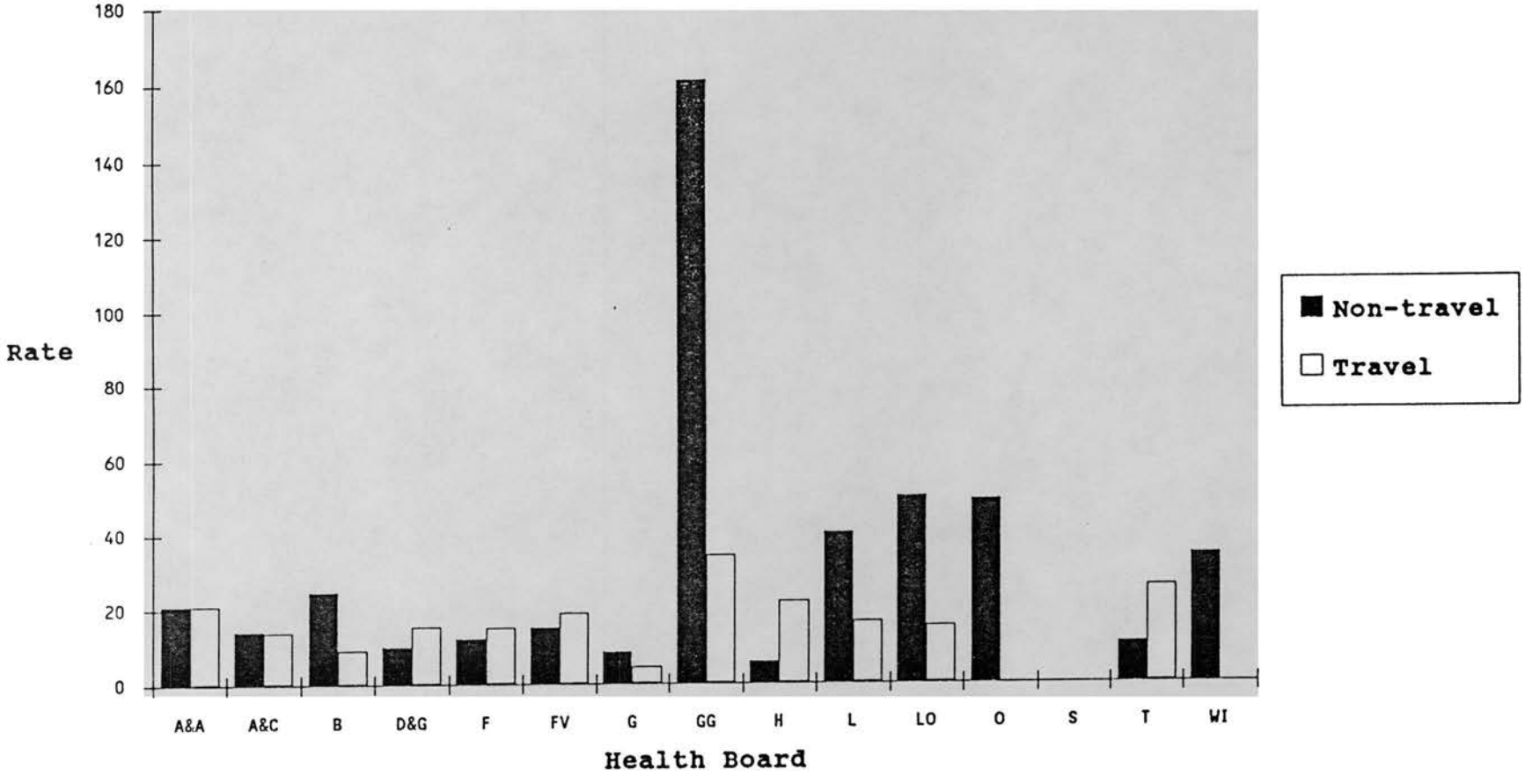


TABLE 4.7

THE NUMBERS AND CUMULATIVE INCIDENCE RATES (ADJUSTED FOR AGE AND SEX) OF TRAVEL AND NON-TRAVEL ASSOCIATED CASES BY HEALTH BOARD, 1978 TO 1986

Health Board	Travel associated cases		Non-travel associated cases		All cases	
	Number	Rate/ million	Number	Rate/ million	Number	Rate/ million
Argyll and Clyde	6	13.7	6	14.1	12	27.8
Ayr and Arran	8	21.1	8	21.0	16	42.1
Borders	1	9.1	3	24.5	4	33.6
Dumfries and Galloway	3	15.4	2	9.9	5	25.3
Fife	5	15.1	4	12.0	9	27.1
Forth Valley	5	18.8	4	15.1	9	33.9
Grampian	2	4.5	4	8.5	6	13.0
Greater Glasgow	36	34.4	167	160.6	203	195.0
Highland	4	22.0	1	5.6	5	27.6
Lanarkshire	9	16.5	23	40.4	32	56.9
Lothian	11	15.4	36	49.9	47	65.3
Orkney	0	0.0	1	49.0	1	49.0
Shetland	0	0.0	0	0.0	0	0.0
Tayside	10	25.8	4	10.5	14	36.3
Western Isles	0	0.0	1	34.4	1	34.4
TOTAL	100	19.4	264	51.3	364	70.7

TABLE 4.8

CUMULATIVE INCIDENCE (NUMBER) OF NON-TRAVEL LEGIONNAIRES' DISEASE BY HEALTH BOARD AFTER EXCLUDING OUTBREAK AND NOSOCOMIAL CASES (1978 TO 1986)

Health Board	Community Outbreak Cases excluded	Nosocomial Outbreak Cases excluded
Argyll and Clyde	14.1 (6)	11.7 (5)
Ayr and Arran	21.0 (8)	10.4 (4)
Borders	24.5 (3)	24.5 (3)
Dumfries and Galloway	9.9 (2)	9.9 (2)
Fife	12.0 (4)	12.0 (4)
Forth Valley	15.1 (4)	15.1 (4)
Grampian	8.5 (4)	6.2 (3)
Greater Glasgow	129.6 (135)	114.4 (119)
Highland	5.6 (1)	0.0 (0)
Lanarkshire	33.3 (19)	31.6 (18)
Lothian	49.9 (36)	48.5 (35)
Orkney	49.0 (1)	4.9 (1)
Shetland	0.0 (0)	0.0 (0)
Tayside	10.5 (4)	10.5 (4)
Western Isles	34.4 (1)	34.4 (1)
Total	44.9 (231)	39.4 (203)

TABLE 4.9

RELATIVE RISK OF INFECTION IN GREATER GLASGOW COMPARED TO THE REST OF SCOTLAND AND SELECTED HEALTH BOARDS

Comparison Groups	Relative Risk
Travel-associated infection	
Greater Glasgow compared to	
Rest of Scotland	2.2
Lothian	2.2
Lanarkshire	2.1
Tayside	1.3
Argyll and Clyde	2.5
Non-travel infection	
Greater Glasgow compared to	
Rest of Scotland	6.9
Lothian	3.2
Lanarkshire	4.0
Tayside	15.3
Argyll and Clyde	11.4
Non-travel, non-outbreak infection	
Greater Glasgow compared to	
Rest of Scotland	5.6
Lothian	2.6
Lanarkshire	3.9
Tayside	12.3
Argyll and Clyde	9.2
Non-travel, non-outbreak, community acquired infection	
Greater Glasgow compared to	
Rest of Scotland	5.6
Lothian	2.4
Lanarkshire	3.6
Tayside	10.9
Argyll and Clyde	9.8

related infection residents of the Greater Glasgow Health Board were about twice as likely to develop Legionnaires' Disease as the rest of Scotland and most health boards. For non-travel infection the corresponding ratio was almost seven and varied greatly from one health board to another. The disparity between the relative risks for Greater Glasgow compared to Tayside Health Board for travel (1.3) and non-travel related infection (15.2) is striking.

The frequency of Legionnaires' Disease in Greater Glasgow fluctuated throughout the period to 1986 as table 4.10 shows. The high numbers for non-travel cases in 1984 and 1985 together with the sudden decline in 1986 are particularly notable. Lothian Health Board had an incidence rate higher than Glasgow in 1982 (14.6 per million compared to 3.0 per million) and 1983 (21 per million compared to 16 per million) but few cases in other years. All four non-travel cases in Grampian Health Board occurred in 1984. These and other observations on space time clustering are considered in more detail in section V. The annual fluctuations in travel-associated cases were less marked (table 4.10).

The data in tables 4.7 to 4.10 suggest that there was a marked variation in space and time. These were not simply chance results. For example, the probability of having 119 or more cases of non-travel, non-

TABLE 4.10

NUMBERS OF LEGIONNAIRES' DISEASE CASES IN SELECTED HEALTH BOARDS BY YEAR AND TRAVEL HISTORY

	Year									
Health Board	1978	1979	1980	1981	1982	1983	1984	1985	1986	Total
1. Travel Associated cases										
Greater Glasgow	5	7	5	1	5	4	5	2	2	36
Lothian	0	2	2	1	1	2	1	1	1	11
Lanarkshire	0	0	1	0	1	2	2	0	3	9
Ayr and Arran	0	0	0	1	1	0	2	0	4	8
Tayside	1	3	2	0	0	2	0	0	2	10
2. Non-travel cases										
Greater Glasgow	7	16	5	5	3	16	72	41	2	167
Lothian	2	0	2	0	11	16	2	1	2	36
Lanarkshire	2	2	3	1	1	1	5	6	2	23
Grampian	0	0	0	0	0	0	4	0	0	4

nosocomial, non-outbreak cases in Greater Glasgow, given the distribution for Scotland, was less than 0.00005 (Poisson distribution; adjusted for multiple comparisons). The health boards with a low incidence which was statistically significant after adjustment for multiple comparisons were:

Ayr and Arran	($p < 0.008$)
Argyll and clyde	($p < 0.007$)
Fife	($p < 0.04$)
Grampian	($p < 0.0002$)
Highland	($p < 0.006$)
Tayside	($p < 0.004$).

By comparison, for travel-related infection, Greater Glasgow had a high incidence which could not be explained by chance ($p < 0.02$) but no health board had an incidence which was significantly low.

ii. Cities, towns and villages

The city, town or village of residence was derived from the address or postcode. Forty-four places in Scotland had had one or more travel-associated cases. In comparison, the non-travel associated cases were in 49 places. Table 4.11 shows the numbers of cases and rates per million, by history of travel, for those places with either three or more non-travel cases or two or more travel-related cases over the period 1978-1986. The City of Glasgow ranked first in both categories and accounted for 48% of cases but had 14.9% of the

TABLE 4.11

NUMBER OF CASES AND RATES PER MILLION IN SELECTED CITIES AND TOWNS BY TRAVEL HISTORY, 1978 - 1986

	Number	Cumulative incidence rate	Number	Cumulative incidence rate	Number	Cumulative Incidence rate
	Non-travel cases		Travel cases		Total	
Aberdeen	2	11	2	11	4	21
Alloa	0	0	2	76	2	76
Ayr	3	61	0	0	3	61
Clydebank	4	77	0	0	4	77
Coatbridge	0	0	3	59	3	59
Cumbernauld	4	84	0	0	4	84
Dundee	4	23	5	29	9	52
East Kilbride	3	42	3	42	6	85
Edinburgh	31	74	6	14	35	83
Glasgow	150	196	27	35	177	231
Greenock	1	17	2	34	3	51
Inverness	0	0	2	50	2	50
Milngavie*	2	166	2	166	4	332
Paisley	1	12	2	24	3	35
Perth	0	0	2	47	2	47
Renfrew	3	140	0	0	3	140
Uphall**	0	0	2	-	2	-
Wishaw	4	106	1	26	5	131

* Population was 12,067.
** This town is not listed in the Registrar General's listing of localities which have a population of >1000.

population. (For other cities the rate of non-travel associated disease did not correspond well with the number of travel cases). Edinburgh and Glasgow had 68% of the non-travel cases compared to 33% of the travel-associated cases (Glasgow had 56% of the former and 27% of the latter). These data again confirm that variation of incidence of non-travel cases was greater than for travel cases.

As for health boards, the annual variation in the number of travel-related cases was small, in contrast to the non-travel cases (data not shown). The pattern of distribution of cases was now examined at the post-code sector level.

iii. Postcode Sector

The cumulative age, sex standardised incidence rates for the period 1978 to 1986 were calculated for postcode sectors in Scotland (approximately 900 in total). The postcode sectors where the number of non-travel cases was significantly high ($P<0.01$) are listed in table 4.12, together with the numbers of cases, the cumulative incidence rate, the ratio of the observed to expected number of cases (standardised for age and sex) and the probability of this number of cases occurring by chance, both before and after adjustment for multiple comparisons. These 16 sectors alone had 89 cases (33% of the total).

TABLE 4.12

POSTCODE SECTORS IN SCOTLAND WITH A HIGH CUMULATIVE INCIDENCE OF NON-TRAVEL LEGIONNAIRES' DISEASE

Postcode sector	No of cases	standardised incidence rate	Standardised morbidity ratio	P1*	P2*
EH6.5	2	494	9.8	<0.01	N.S.
EH7.4	4	416	10.1	<0.0004	N.S.
G3.6	2	489	9.9	<0.0006	N.S.
G4.0	10	913	18.7	<0.0001	<0.0001
G11.5	6	1039	18.1	<0.0001	<0.00001
G12.8	3	609	11.8	<0.003	N.S.
G21.2	4	438	7.9	<0.001	N.S.
G21.4	4	434	5.7	<0.001	N.S.
G22.6	4	354	2.8	<0.002	N.S.
G31.2	17	2459	46.0	<0.0001	<0.0001
G31.3	14	1585	32.0	<0.0001	<0.0001
G31.4	3	461	7.8	<0.001	N.S.
G32.8	4	433	8.8	<0.001	N.S.
G33.3	5	340	7.5	<0.001	N.S.
G60.5	2	530	10.3	<0.010	N.S.
G72.8	5	405	8.3	<0.0001	N.S.

* P1 is the P value unadjusted for multiple comparisons; P2 is adjusted

Of the 16 post-code sectors listed, 14 are in the Greater Glasgow Health Board (G72.8 extends into Lanarkshire Health Board but all cases lived within the Glasgow boundary) and the other two in Edinburgh. (These postcode sectors are shown in the transparencies in the folder in the cover). All four postcode sectors where the high incidence remained statistically significant after adjustment for multiple comparison were within the Greater Glasgow Health Board. The standardised legionella morbidity ratio in post-code sector G31.2 was 46. Excepting G72.8 all the postcode sectors in the Greater Glasgow Health Board listed in table 4.12 are North of the River Clyde.

The analysis was repeated for travel-related infection. As shown in table 4.13 which lists the sectors with a high incidence ($p< 0.02$) in no instance was the adjusted p value less than 0.05. Five of the eight postcode sectors with a high incidence ($p< 0.02$) were in Greater Glasgow.

Table 4.14 gives the results of an analysis of the Greater Glasgow Health Board data where the incidence rates were standardised on the age and sex distribution of the Greater Glasgow population, by travel and outbreak history. For travel-related disease evidence of clustering was found in four postcode secors but in none was it statistically significant after adjustment for

TABLE 4.13

POST-CODE SECTORS IN SCOTLAND WITH A HIGH CUMULATIVE INCIDENCE OF TRAVEL-ASSOCIATED LEGIONNAIRES' DISEASE

Post-code sector	No of Cases	Standardised incidence rate	Standardised morbidity ratio	P1	P2
FK102	2	177	8.0	<0.02	N.S.
G12.9	2	378	15.6	<0.005	N.S.
G14.9	2	161	8.7	<0.003	N.S.
G43.2	3	296	11.5	<0.002	N.S.
G44.5	3	362	16.3	<0.0006	N.S.
G73.3	2	238	11.1	<0.008	N.S.
IVI.1	1	585	31.0	<0.02	N.S.
ML5.3	2	409	19.3	<0.004	N.S.

TABLE 4.14

POSTCODE SECTORS IN GREATER GLASGOW HEALTH BOARD WITH A HIGH INCIDENCE OF LEGIONNAIRES' DISEASE BY TRAVEL HISTORY, WITH AND WITHOUT OUTBREAK CASES

Post-code sector	No of Cases	Standardised Incidence rate	Standardised Morbidity ratio	P1	P2
Travel Cases					
G43.2	2	273	6.7	<0.007	N.S.
G44.5	3	273	9.2	<0.003	N.S.
G12.9	2	256	9.0	<0.002	N.S.
G73.3	2	236	6.4	<0.003	N.S.
Non-travel Cases					
G4.0	10	1664	6.3	<0.001	<0.001
G11.5	6	923	5.8	<0.001	<0.007
G31.2	17	2154	14.7	<0.001	<0.001
G31.3	14	1682	10.5	<0.001	<0.001
Non-travel, non-outbreak community-acquired cases					
G4.0	9	841	7.7	<0.0001	<0.0004
G11.5	6	1049	7.9	<0.0001	<0.02
G21.2	4	429	3.5	<0.02	N.S.
G21.4	4	444	3.6	<0.02	N.S.
G31.3	4	407	4.1	<0.001	N.S.
G32.8	4	453	3.9	<0.02	N.S.
G72.8	5	412	3.7	<0.01	N.S.

multiple comparisons. One of these postcode sectors lies north of the River Clyde (G12.9) and three lie south. Of the non-travel cases, there was clustering in four post-code sectors, all north of the river, and the high incidence remained statistically significant in three postcode sectors after adjustment for multiple comparisons. When outbreak and nosocomial cases were excluded and only non-travel cases considered, seven post-code sectors stood out, all but one north of the R. Clyde. Furthermore, it appeared that the post-code sectors adjoining those sectors with a high incidence also had more cases than expected, though not at a statistically significant level. Hence, further analysis was done by plotting the distribution of all cases and preparing chloropleth maps based on post-code sectors by health board. (A transparency showing the post-code sectors is provided in the back folder).

iv. Point-pattern and chloropleth mapping

The point-pattern map in figure 4.4 shows the location of residence of travel-related cases within Greater Glasgow. Other than the cluster of three cases in G44.5 and the case adjacent in G73.4, there is no obvious clustering. These cases were not clustered in time. The chloropeth map in figure 4.4 confirms that the incidence of travel-associated infection was low in and adjacent to the city centre post-code sectors and that the highest rates were in the residential areas

FIGURE 4.4 MAPS OF RESIDENCE OF TRAVEL-RELATED LEGIONNAIRES' DISEASE CASES IN GGHB.

outside the city centre (we have already seen that the rate was not significantly high in any sector).

The point-pattern map in figure 4.5 gives the location of residence for non-travel cases and shows marked clustering. As expected the clustering is most marked in post-code sectors G4, G11.5, G31.2 and G31.3 but also in adjoining areas. The concentration of cases is in the city centre and adjacent to the River Clyde. In addition there are clusters of cases in G72.8, G73.4, G60.5 and G81.4. Figure 4.5 (chloropleth map) shows that people living in or near the city centre are at greatest risk of infection and that of the post-code sectors with a high incidence (exceeding 450 per million) all but one are North of the River Clyde and the exception lies adjacent to it. Figure 4.6 shows that after outbreak and nosocomial cases have been excluded, the pattern remains similar i.e. the incidence is highest in the central post-code sectors. Figure 4.7 is a probability map based on non-travel, non-outbreak cases which highlights the post-code sectors with a high incidence of infection and shows the probability of that incidence being a result of chance. The central clustering was observed in several years (figure 4.8) and in particular both before and after 1984 (figure 4.9).

The workplace and residence was known for 28 of the Greater Glasgow cases. In figure 4.10 the workplace and

FIGURE 4.5 **MAPS OF THE RESIDENCE OF NON-TRAVEL LEGIONNAIRES' DISEASE CASES IN GGHB.**

FIGURE 4.6 MAPS OF THE RESIDENCE OF COMMUNITY-ACQUIRED, NON-TRAVEL LEGIONNAIRES' DISEASE CASES IN GGHB.

FIGURE 4.7 PROBABILITY MAP OF THE RESIDENCE OF COMMUNITY-ACQUIRED, NON-TRAVEL, NON-OUTBREAK LEGIONNAIRES' DISEASE CASES IN GGHB.

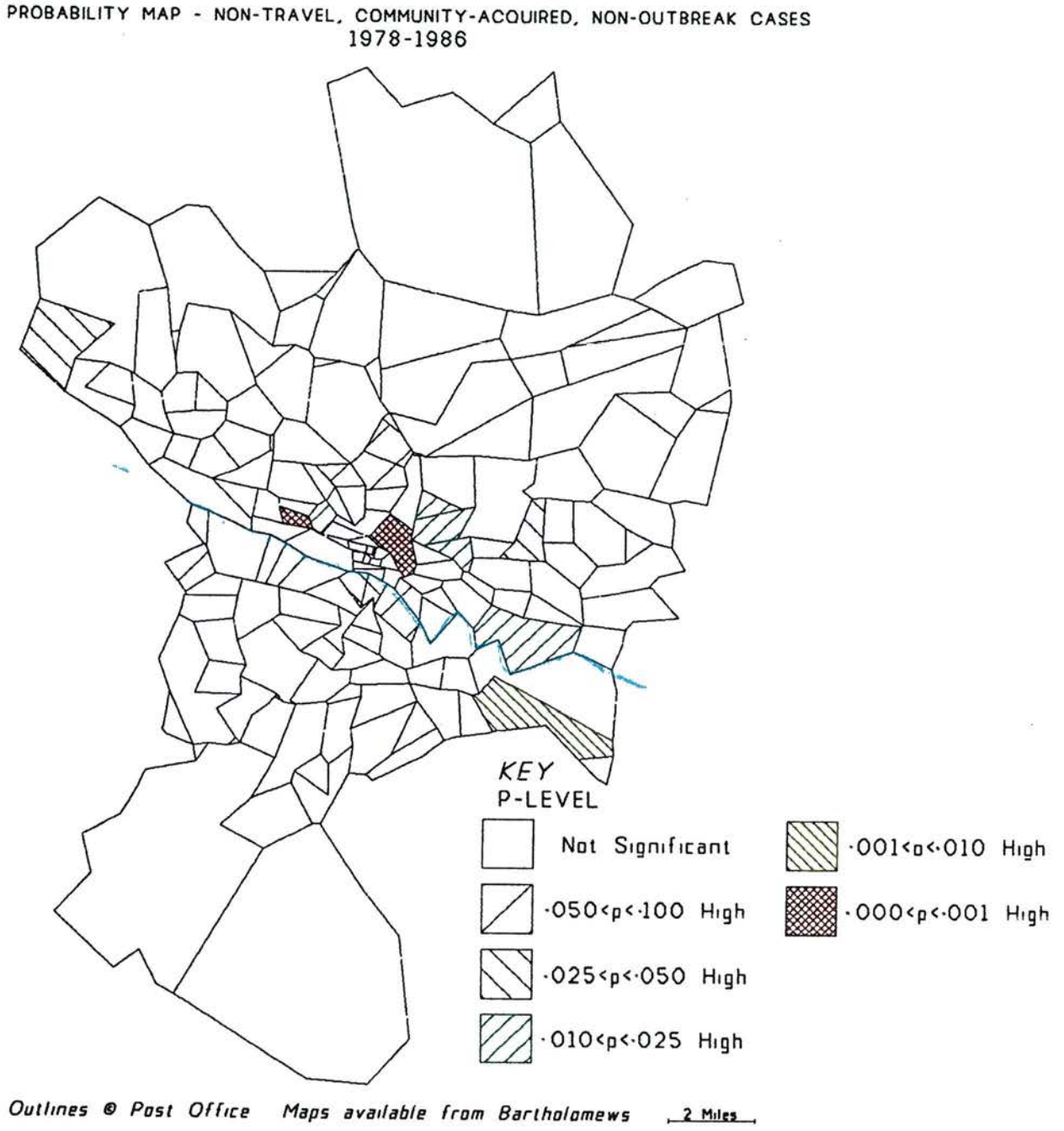


FIGURE 4.8 MAPS OF THE RESIDENCE OF NON-TRAVEL LEGIONNAIRES' DISEASE CASES IN GGHB, BY YEAR.

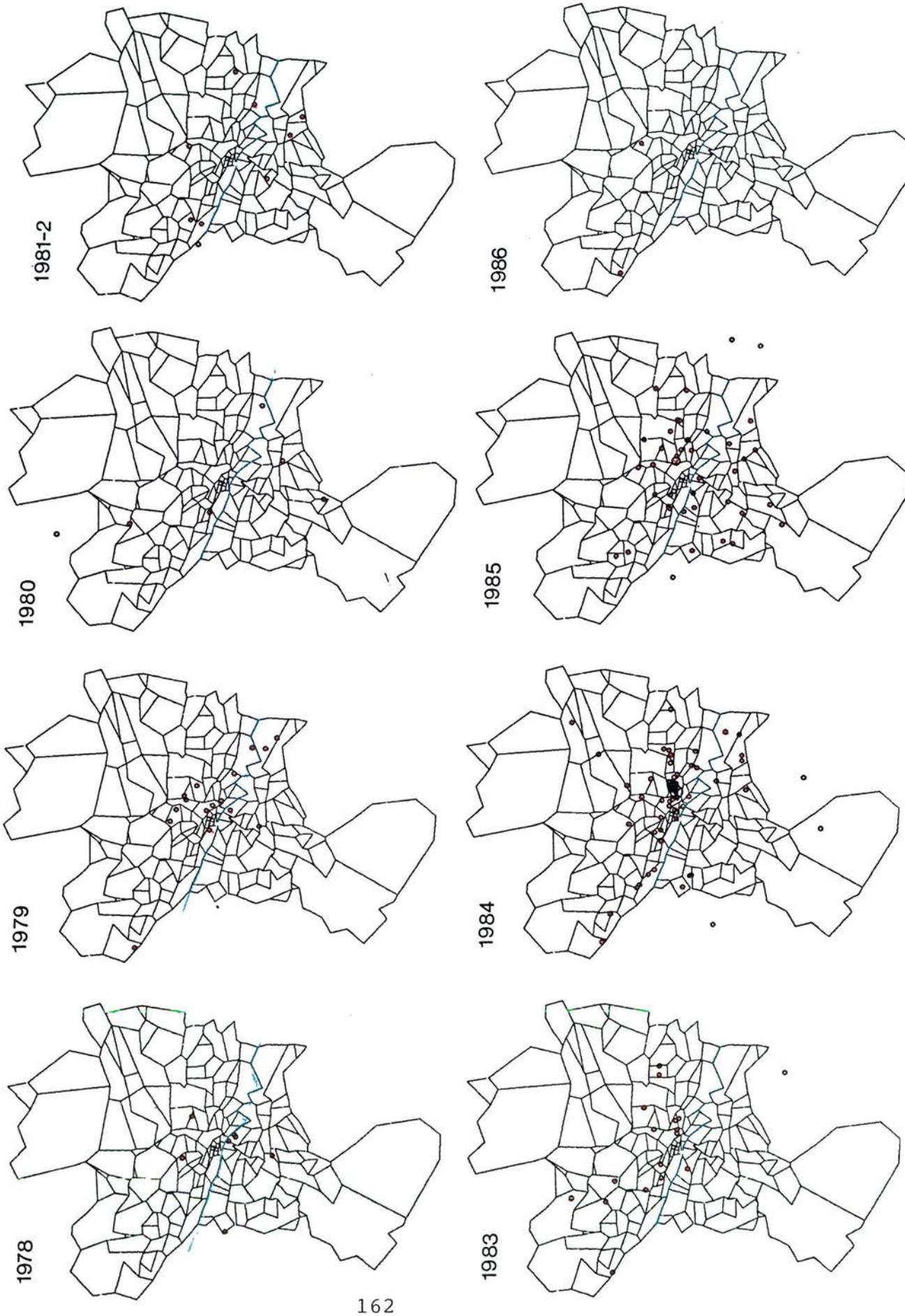


FIGURE 4.9 MAPS OF THE RESIDENCE OF COMMUNITY-ACQUIRED, NON-TRAVEL, NON-OUTBREAK LEGIONNAIRES' DISEASE CASES IN GGHB, BEFORE AND AFTER 1984.

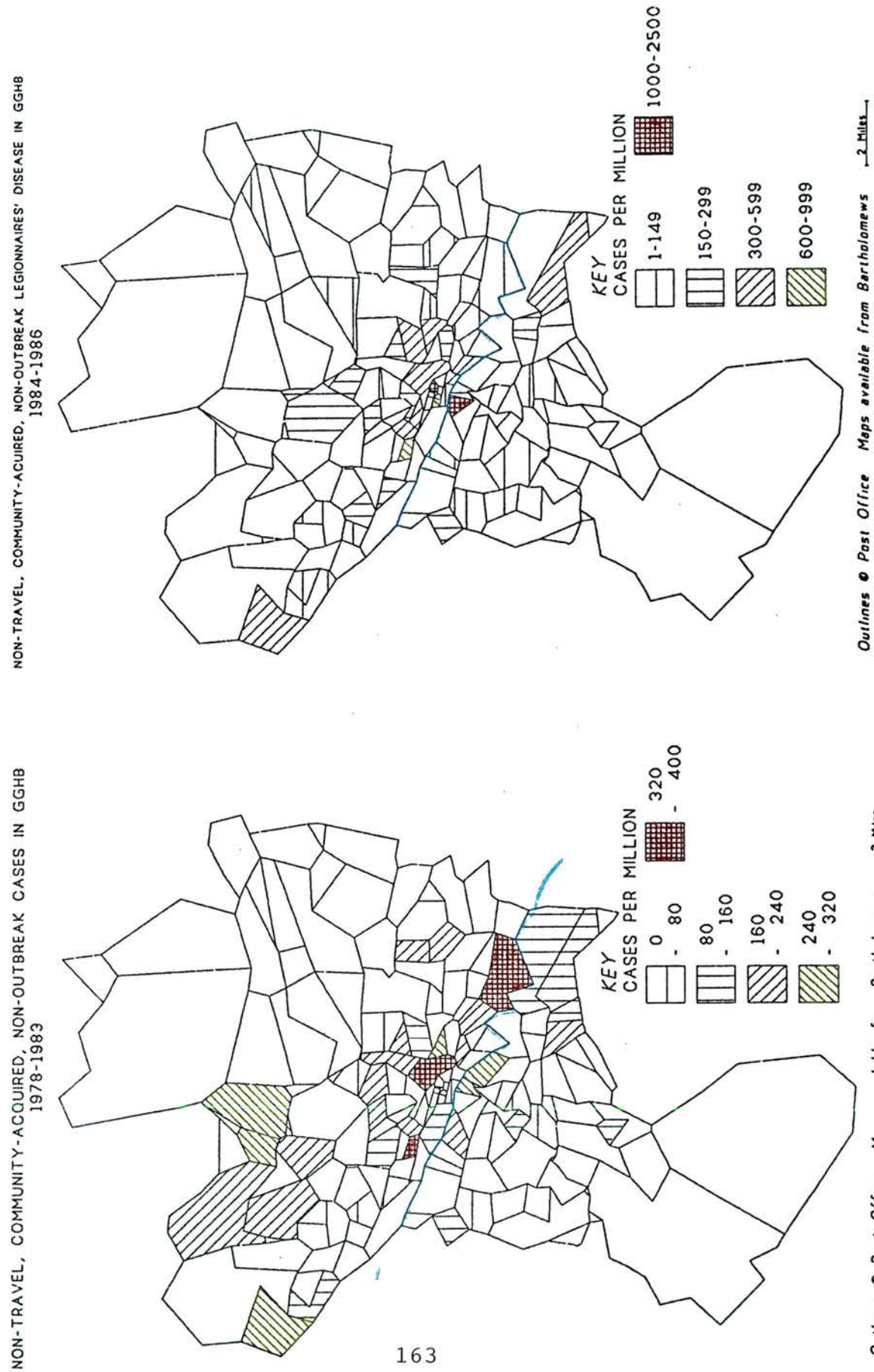
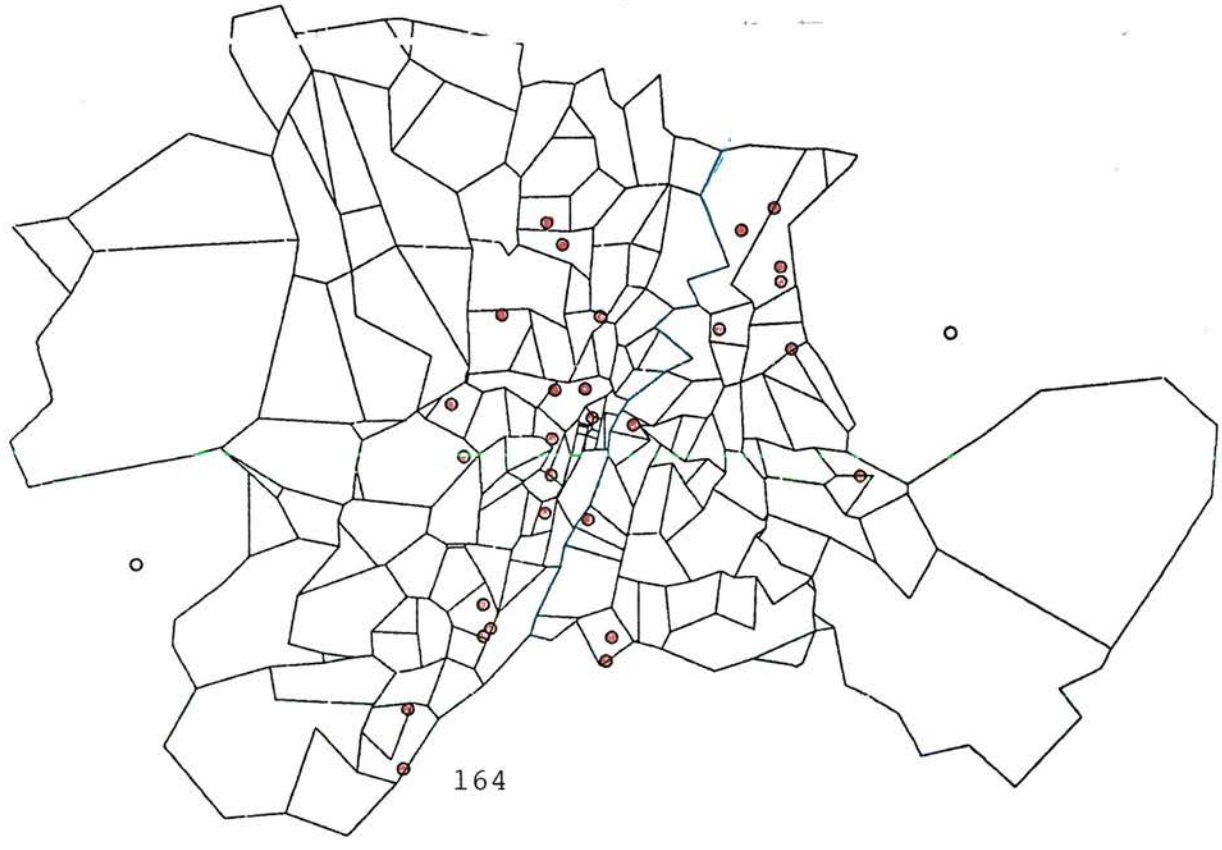


FIGURE 4.10 MAPS OF THE RESIDENCE AND WORKPLACE OF A SUBGROUP OF NON-TRAVEL, COMMUNITY-ACQUIRED LEGIONNAIRES' DISEASE CASES IN GGHB.

RESIDENCE OF NON-OUTBREAK, NON-TRAVEL CASES - GGHB RESIDENTS ONLY
1978-1986



RESIDENCE OF NON-OUTBREAK, NON-TRAVEL CASES WHOSE WORKPLACE WAS KNOWN WORKPLACE OF NON-OUTBREAK, NON-TRAVEL CASES - GGHB RESIDENTS ONLY
1978-1986

residence are compared and it is apparent that most of these people worked closer to the city centre than they lived. Further, the workplace of these cases showed clustering, in the areas east and west of the city centre itself. (Unfortunately, no comparison group was available).

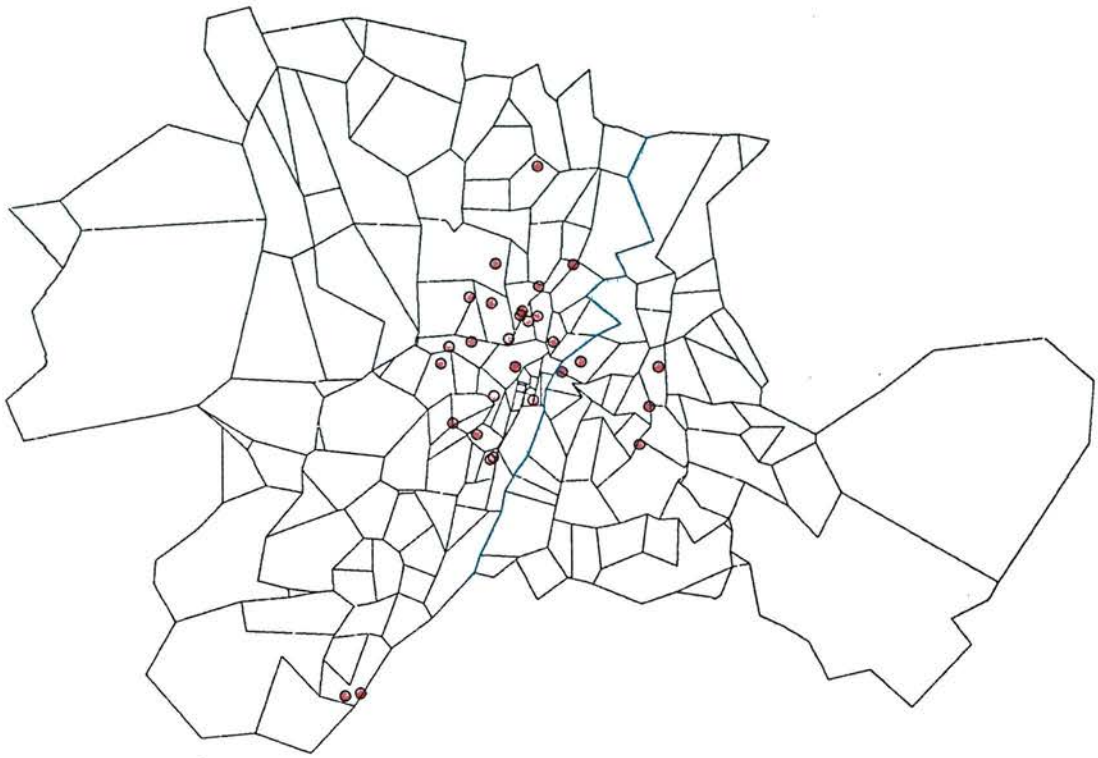
Figure 4.11 and 4.12 show that the demonstrated central clustering of Legionnaire's Disease, is not exclusive to those of working age or men but applies to those over 65 years and to both sexes.

Similar analyses were done for Lothian Health Board and the City of Edinburgh. The small number of cases preclude definite conclusions but the findings were of interest. Figure 4.13 shows that the pattern of travel and non-travel cases in Lothian was different; most travel-related cases resided distant to the centre of Edinburgh City. In contrast the non-travel cases were clustered around the city of Edinburgh, particularly in northern and central areas. Figure 4.14 shows the pattern within the city, for travel and non-travel cases respectively. There was no clustering of travel-related infection but a cluster of non-travel cases is apparent in post-code sectors EH 7.4 and EH 6.5 (see below).

A more detailed examination of space-time clustering was now done.

FIGURE 4.11 MAPS OF THE RESIDENCE OF COMMUNITY-ACQUIRED, NON-TRAVEL, NON-OUTBREAK LEGIONNAIRES' DISEASE CASES IN GGHB FOR TWO AGE GROUPS.

NON-TRAVEL, NON-OUTBREAK CASES AGED MORE THAN 65 YEARS



NON-TRAVEL, NON-OUTBREAK, COMMUNITY-ACQUIRED CASES
0-64 YEARS

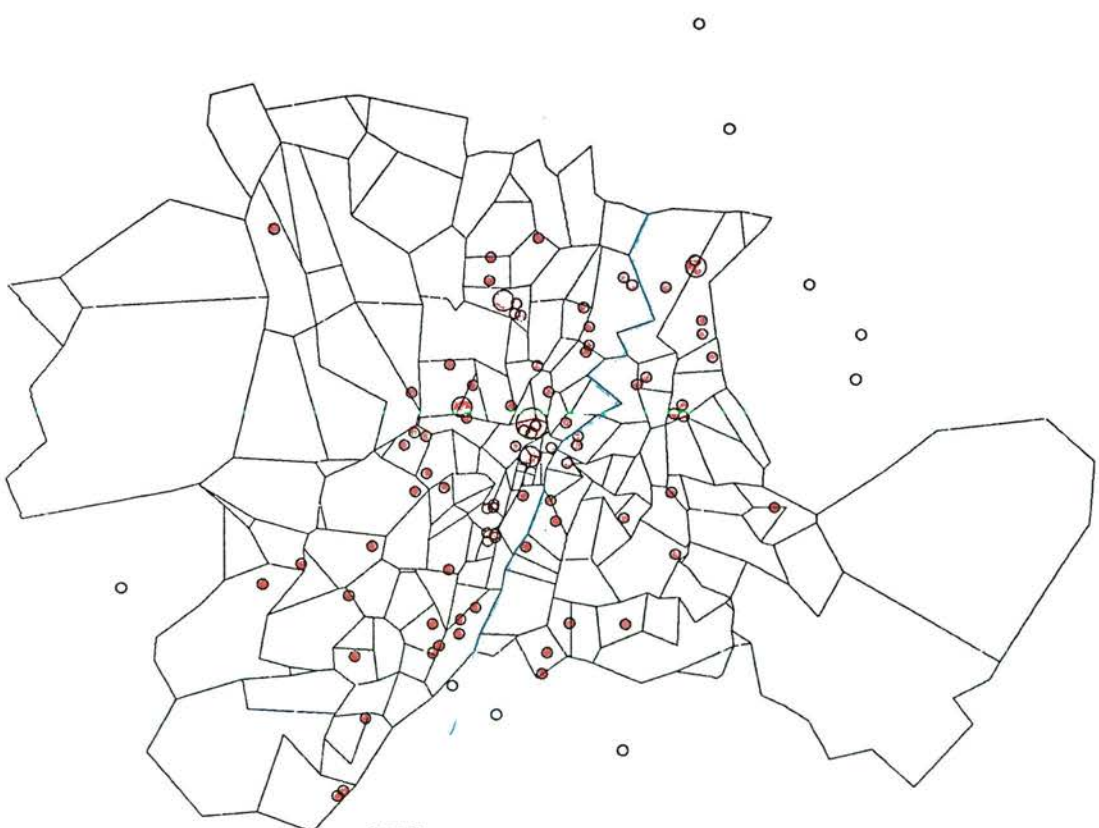
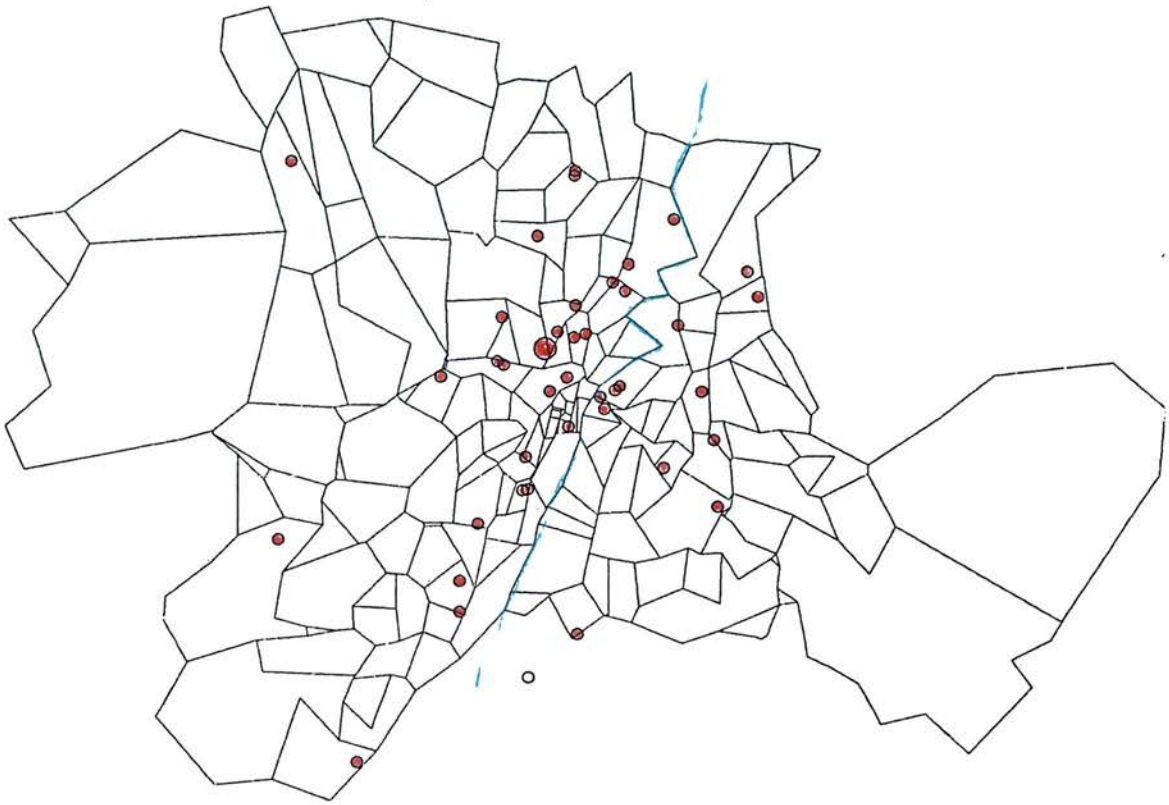


FIGURE 4.12 **MAPS OF THE RESIDENCE OF COMMUNITY-ACQUIRED, NON-OUTBREAK LEGIONNAIRES' DISEASE CASES IN GGHB, BY GENDER.**

NON-TRAVEL, NON-OUTBREAK FEMALE CASES 1978-1986



NON-TRAVEL, NON-OUTBREAK MALE CASES 1978-1986

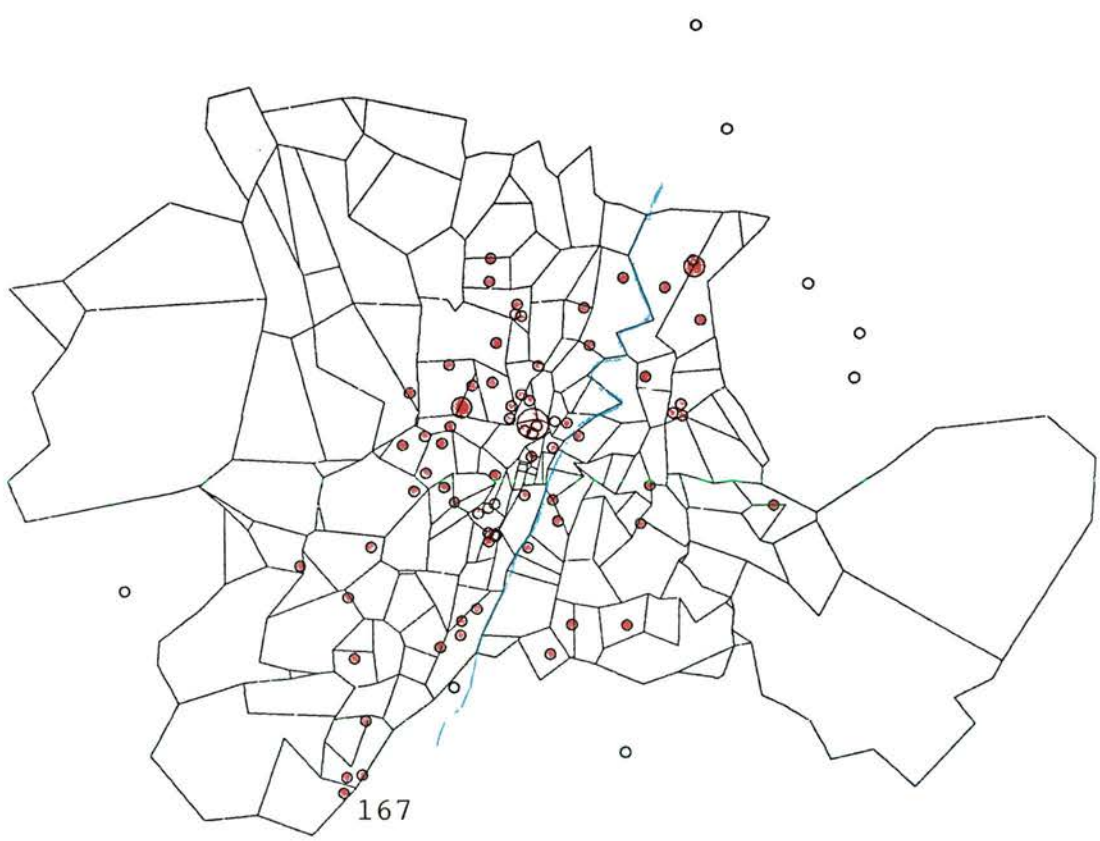
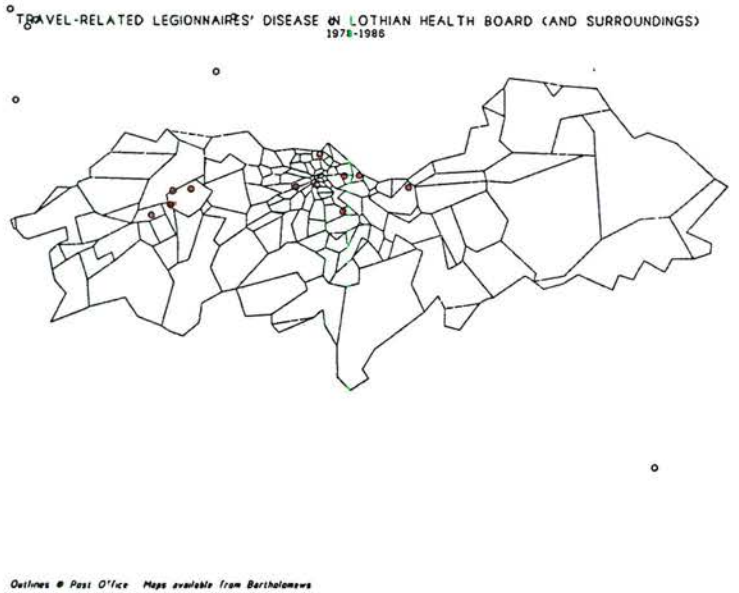
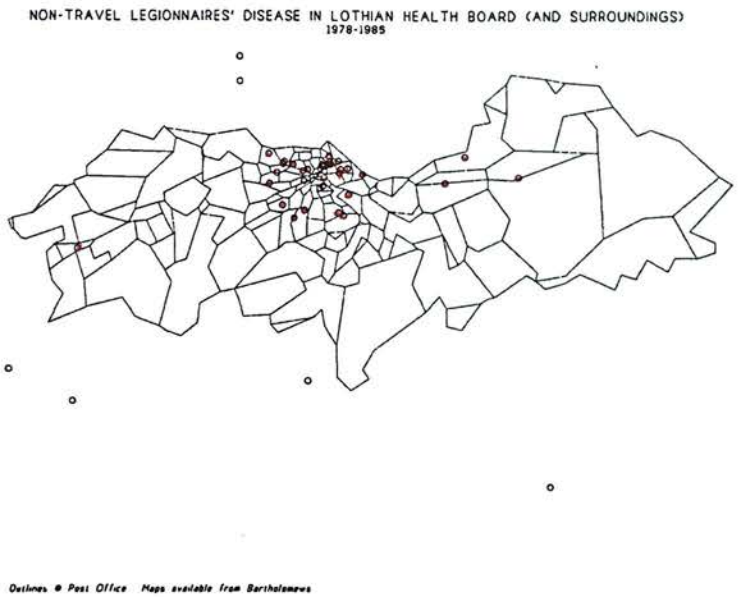
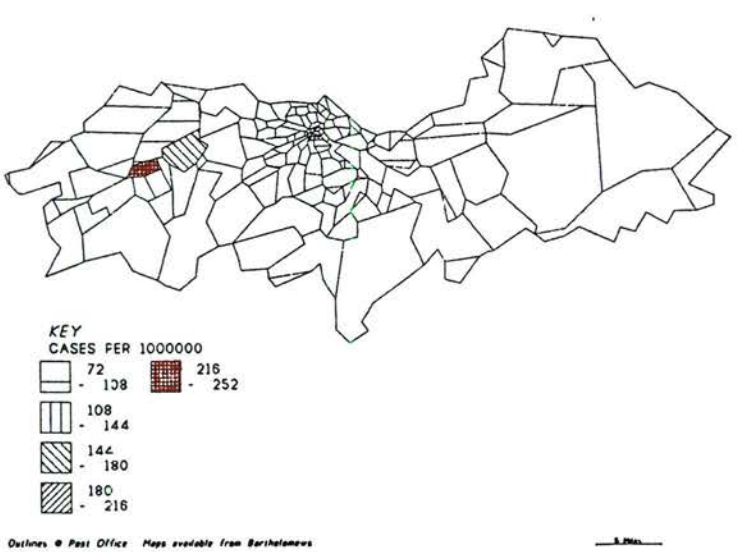


FIGURE 4.13 MAPS OF THE RESIDENCE OF LEGIONNAIRES' DISEASE CASES IN LOTHIAN HEALTH BOARD, BY TRAVEL HISTORY.







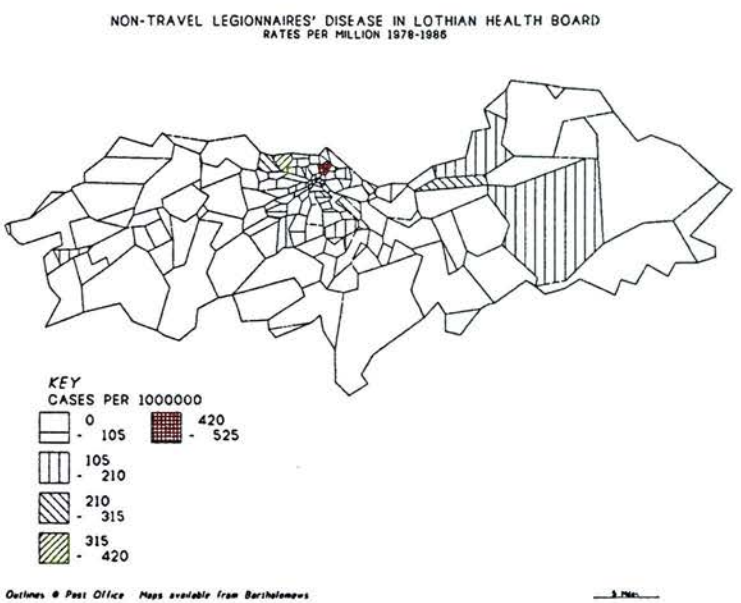
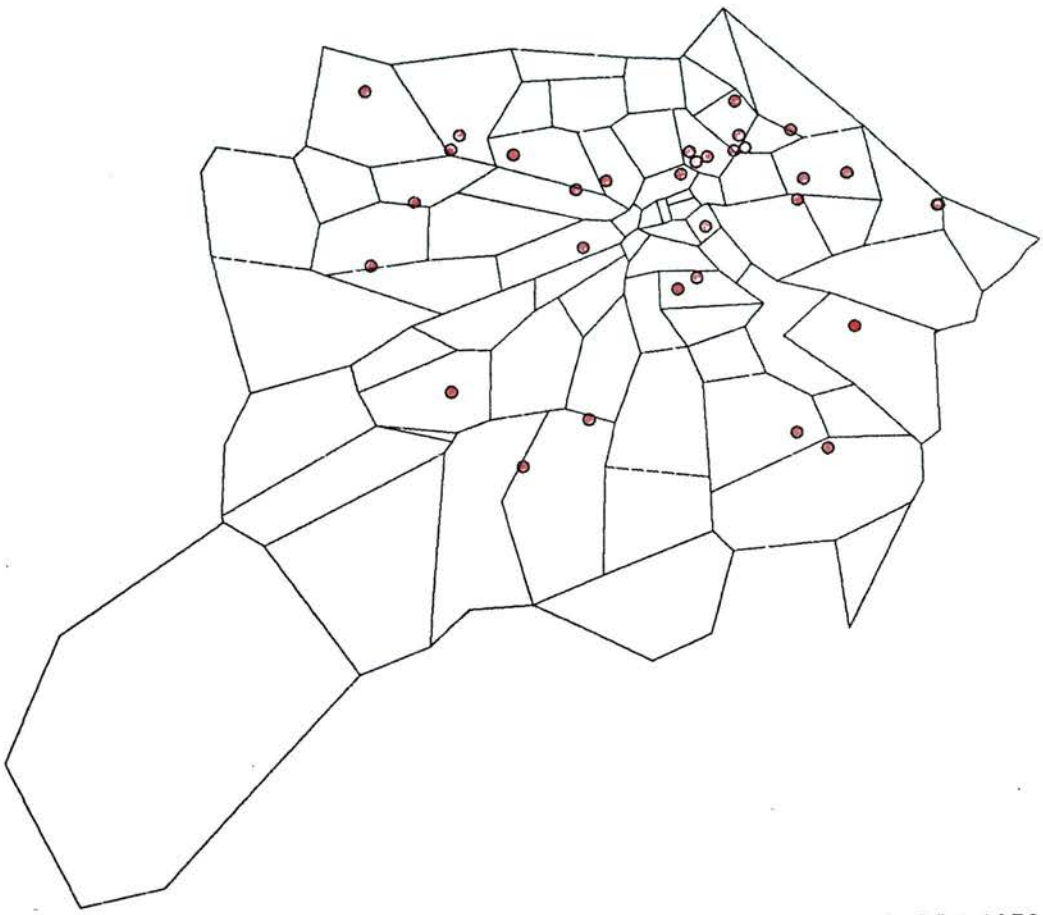
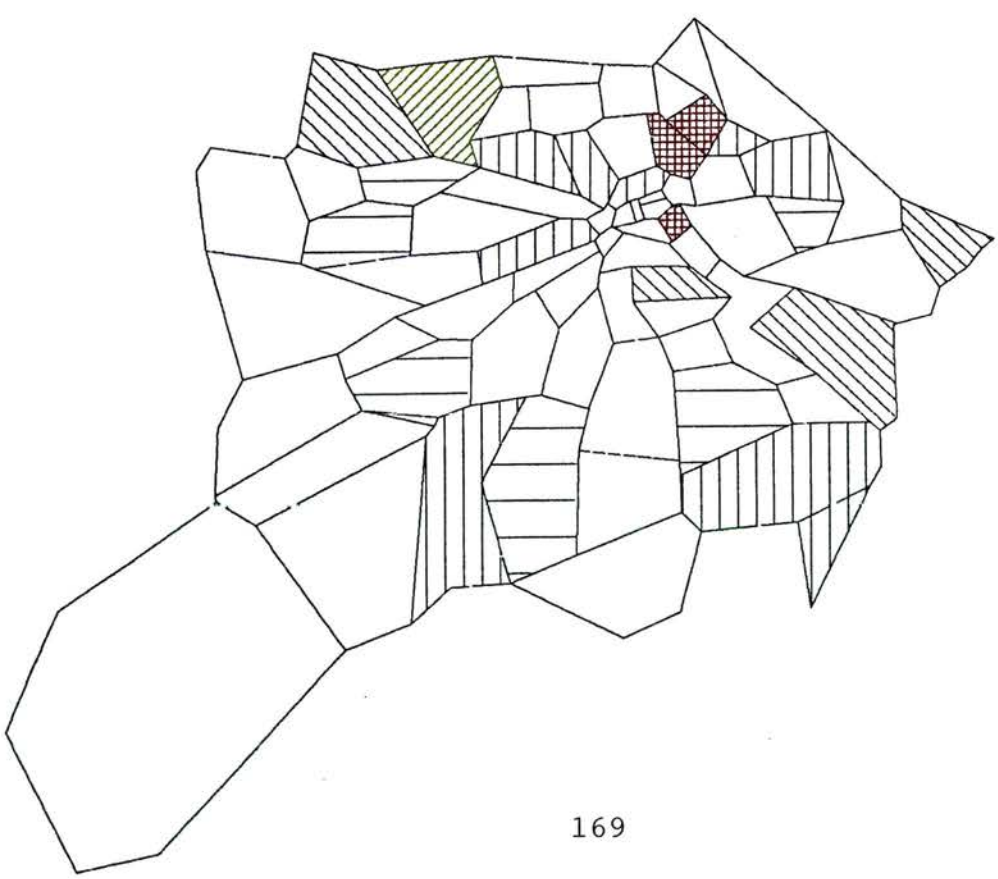


FIGURE 4.14 MAPS OF THE RESIDENCE OF NON-TRAVEL LEGIONNAIRES' DISEASE IN EDINBURGH CITY.

COMMUNITY-ACQUIRED, NON-TRAVEL, LEGIONNAIRES' DISEASE CASES
EDINBURGH CITY 1978-1986



NON-TRAVEL LEGIONNAIRES' DISEASE IN EDINBURGH 1978-1986
RATES PER MILLION



v Clustering in time and space

Legionnaires' Disease is rare, so when two or more cases are clustered in either time or space, there is a suspicion that there is an underlying link between them. When two or more cases are clustered in both time and space, a common link is probable.

Table 4.15 shows the number of non-travel cases in each health board by year of onset. As the footnotes to the table indicate space-time clustering was common e.g. there was spatial clustering of the three cases in Ayrshire and Arran in 1981/1982 and space-time clustering for the 1982 cases, the two Dumfries and Galloway cases were in August and September 1980 in adjoining postcode sectors, and the Tayside cases were also similarly clustered. Due to the two missing addresses for the Grampian cases, comment on spatial clustering could not be made. The most important potential clusters in time were these:

16 cases in Greater Glasgow in 1979 and 1983, 72 cases in 1984 (of which 32 were part of an outbreak) and 41 cases in 1985 (of which 5 were part of an outbreak);

The 5 cases in Lanarkshire Health Board in 1984 and 6 in 1986;

and, the 11 cases in Lothian Health board in 1982 and 16 in 1983.

TABLE 4.15

NUMBER OF NON-TRAVEL CASES IN EACH HEALTH BOARD BY YEAR

HEALTH BOARD	1978	1979	1980	1981	1982	1983	1984	1985	1986	Total
Argyll and Clyde	0	1	0	1	1	0	1	2[a]	0	6
Ayrshire and Arran	0	0	0	1[b]	2[b]	1	0	4[c]	0	8
Borders	1	0	0	0	0	0	1	1	0	3
Dumfries and Galloway	0	0	2[d]	0	0	0	0	0	0	2
Fife	0	0	0	1	1	0	0	1	1	4
Forth Valley	0	0	1	0	2[e]	0	0	0	1	4
Grampian	0	0	0	0	0	0	4[f]	0	0	4
Greater Glasgow	7	16	5	5	3	16	72	41	2	167[g]
Highland	0	0	0	0	0	0	0	1	0	1
Lanarkshire	2	2	3	1	1	1	5	6	2	23[g]
Lothian	2	0	2	0	11	16	2	1	2	36[g]
Orkney	0	0	0	1	0	0	0	0	0	1
Tayside	0	0	2[h]	0	0	1[i]	0	1[i]	0	4
Western Isles	0	1	0	0	0	0	0	0	0	1
TOTAL	12	20	15	10*	21	35	85	58*	8	264

a) One was nosocomial

(b) All three of these cases were in one postcode sector (KAB) and the two in 1982 were both in August

(c) All four were nosocomial

(d) Adjoining postcode sectors and in August and September 1980

(e) Separated in time and space

(f) One was a possible nosocomial case. These 4 cases had date of onset in January, July, September and October 1984, two postcode were known - these were spatially apart

(g) See tables 4.16, 4.17, and 4.18

(h) Dates of onset were May and June 1980 and the case lived in adjacent postcodes

(i) These two cases, though separated by 2 years, were in the same postcode sector, one adjoining those cases in (h)

* These figures are not the same as in table 4.4 because for two of the cases analysis by health board was inappropriate; they were from England.

Tables 4.16, 4.17, and 4.18 give the number of cases by year and month of onset in Greater Glasgow, Lothian and Lanarkshire Health Boards respectively and the footnotes record whether spatial clustering was observed. Clearly space-time clusters did occur but had not been associated with outbreaks as summarised below.

In Greater Glasgow the two cases in October and November of 1978 were in the G5.0 postcode and the one in November in G5.9, the four pairs of cases in 1983 were either in the same or adjacent postcode sectors, the two cases in February 1984 were in contiguous postcode sectors, the five cases in 1984 were in G4.0 and the 5 cases in 1985 were in the G21 and G22 area. Six cases occurred in the G31 postcode district over the period October 1984 to November 1985, after the outbreak in that area was adjudged to have been controlled (Ad-hoc Committee, 1986). In the postcode areas G11 and G12 there occurred 10 cases on the period 1980 to 1985 as follows: one in 1980; one in February and two in November 1980; three in August 1984 and one in October 1984; one in each of March and April 1985.

In Lothian Health Board too there was space-time clustering e.g. two cases in the EH 9.1 postcode sector with a date of onset in August and September 1982, the three cases in EH 4.2 and EH 4.7 in the period July to September 1982, and the 9 cases in EH 6 and EH 7 between May and December 1983.

TABLE 4.16

NUMBER OF NON-TRAVEL CASES IN GREATER GLASGOW HEALTH BOARD BY YEAR AND MONTH*

Year	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	Total
1978(a)	0	0	0	1	1	0	1	0	0	1	3	0	7
1979(b)	0	0	0	0	3	0	2	4	3	0	3	0	15
1980(c)	1	0	0	0	0	0	0	1	2	0	1	0	5
1981(c)	1	0	0	1	0	1	0	0	1	1	0	0	5
1982(c)	0	0	0	0	0	1	1	0	0	1	0	0	3
1983(d)	2	2	0	0	0	0	1	1	3	0	6	1	16
1984(e)	0	2	3	0	1	26	4	4	6	7	7	12	72
1985(f)	4	7	1	2	1	1	1	0	1	8	10	5	41
1986(c)	0	0	0	0	0	0	0	0	0	1	1	0	2
Total	8	11	4	4	6	29	10	10	16	19	31	18	166

* For one case neither the month of onset nor the date of serology were known

(a) Three of four October/November cases were in G5.

(b) Clustering in space not striking: but see maps in fig 4.8.

(c) No striking clustering.

(d) Two of November cases were in G21.1 and G21.3 (contiguous postcode sectors) while two were in G11.5 and G12.8, also contiguous. The August case and one November case were in G4.0. Similarly, one case in September and a case in December were in G33.5 Other cases were scattered spatially

(e) The two February cases were in G66.2 and G66.4, contiguous postcode sectors.
Most of the cases in June to September were associated with the Dennistoun outbreak. However, 2 cases, one in March and the other in June 1984, occurred in residents of a boarding house in G4.0 adjacent to G31. A further case in G4.0 occurred in October and two more in August. In October and November 1984, two more cases occurred in G31.4 and G31.3, at a time when the Dennistoun outbreak was judged to be over. A third case (G31.1) became ill in January 1985, a fourth in February 1985, and a fifth in April 1985 (G31.3), and a sixth in November 1985 (G31.3).

(f) In January 1985, two patients in contiguous postcodes, G21.2 and G22.6, became ill, and two more were ill in G22.7 and G21.4 in February. Later, in October 1985 another case occurred in G21.2. Of the extra possible nosocomial cases identified during the course of this study (appendix 5), seven were ill between October and December 1985.

TABLE 4.17

NUMBER OF NON-TRAVEL CASES IN LOTHIAN HEALTH BOARD
BY YEAR AND MONTH

Year	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	Total
1978[a]	0	0	1	0	0	1	0	0	0	0	0	0	2
1980[a]	0	0	0	0	0	0	1	0	0	0	0	1	2
1982[b]	0	0	0	0	0	0	3	5	3	0	0	0	11
1983[c]	0	0	0	0	1	0	0	3	1	1	6	4	16
1984*	0	0	0	1	0	0	0	0	0	0	0	0	1
1985	0	1	0	0	0	0	0	0	0	0	0	0	1
1986[a]	0	0	0	0	0	0	1	0	1	0	0	0	2
Total	0	1	1	1	1	1	5	8	5	1	6	5	35

* The month of onset was not known for one of these cases

(a) No clustering.

(b) Two cases in EH9.1 in August and September 1982, and three in EH4.2 and EH4.7 (contiguous) in July, August and September.

(c) Nine cases in EH6 and EH7 (contiguous sectors) between May and December 1983.

TABLE 4.18

NUMBER OF NON-TRAVEL CASES IN LANARKSHIRE HEALTH BOARD
BY YEAR AND MONTH

Year	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	Total
1978[a]	0	0	0	0	2	0	0	0	0	0	0	0	2
1979[a]	0	0	0	0	1	0	0	1	0	0	0	0	2
1980[b]	1	0	0	0	0	0	0	0	0	1	1	0	3
1981	0	0	0	0	0	0	0	0	0	1	0	0	1
1982	0	0	0	0	0	0	0	1	0	0	0	0	1
1983	0	0	0	0	0	0	0	0	0	0	1	0	1
1984[c]	0	0	0	0	0	1	0	0	0	1	1	2	5
1985[d]	0	2	0	0	0	0	0	2	0	1	1	0	6
1986*	0	0	0	0	0	0	0	0	0	0	1	0	1
Total	1	2	0	0	3	1	0	4	0	4	5	2	22

* For one case the month of onset was not known

(a) Not spatially clustered

(b) October and November cases in adjacent postcode sectors.

(c) Two cases in G67.1 and G67.2 in November and December 1984 and another in G67.2 in 1986.

(d) Two cases in G71.6 in November and December 1985 (one was nosocomial) and G71.8 in February 1985.

In Lanarkshire Health Board, three of the 1984 cases were in adjacent postcode sectors G 67.1 and G 67.2 in November and December, while two of the non-outbreak 1985 cases were in the adjoining postcode sectors G 71.6 and G 71.8.

Similar analysis for travel-related infection was done. In only one instance was there space-time clustering: two patients lived in G 46.6 and 46.7 (adjoining postcode sectors sectors) and were ill in July 1979. However, these patients had acquired their illnesses in different places.

PRELIMINARY DISCUSSION: ARE THE FINDINGS REAL OR ARTEFACT?

The five principal findings of interest were these: the comparatively high incidence of disease in Scotland, the fluctuation in the annual incidence rate, the unusual seasonal pattern with a winter excess, the marked geographical variation and the previously unrecognised spatio-temporal clusters. These observations are discussed in the final chapter. The age and sex distribution of cases was as reported by others and will not be further discussed.

The key question is whether these observations are artefacts resulting from incorrect case definition, invalid diagnostic methods, faulty data or poor study design. Only if artefact can be excluded is interpretation appropriate.

The case-definition used differed in minor ways from the internationally recognised one of the Centres for Disease Control. Firstly, a fourfold rise in titre of 64, compared to 128, was accepted in support of a diagnosis. This was in accord with British recommendations and based on English and Scottish data that titres above 64 are rare in the British population (Fallon and Abraham,1982b; Taylor,1987; Harrison et al,1987). Secondly, a four-fold fall in titre during convalescence was accepted as evidence of disease.

Though most previous studies have not clarified explicitly the interpretation of a four-fold fall, on general principles it indicates recent infection. In one respect the definition used was stricter than that of most studies i.e. possible dual infections were not classified as cases. Dual infections do occur, both with different species (Woodhead et al,1986b) and with different subgroups of Legionellae (Horbach,1988). However,the interpretation of the evidence in individual cases is difficult. About 10% of the cases did not fit the Centres for Disease Control definition (14 cases had a rising titre to 64, 16 had a four-fold fall, two had a static titre of 64 and the six who had evidence of dual infection). These differences in the case definition do not explain the high incidence of disease in Scotland.

The diagnostic methods used by the Ruchill Hospital Laboratory have been comparable to those elsewhere. A minor controversy over the methods used in the Ruchill laboratory has concerned the use of heat-killed rather than the formalin, ether or phenol-killed antigens (Fallon and Abraham,1982b). However, the heat-killed antigen has been found to be superior to the ether-killed one (Wilkinson et al, 1979) and comparable to formalin-killed and phenol-killed antigens (Fallon and Abraham, 1982b; Pastoris et al,1984; Wilkinson and Brake,1982). Though formalin-killed antigen may give slightly lower serological titres the high incidence in Scotland cannot

be explained on the basis of laboratory methodology. In interpreting time trends in the numbers of cases the type of tests done should be considered in addition to the numbers of tests.

Some of the annual variation in incidence may result from the increasing range of tests available but two observations argue against this being of paramount importance. Firstly, most cases were of serogroup I in all years and the means for detecting this serogroup were available from 1978. Secondly, there was a weak relationship between the annual incidence and number of tests done, dramatically demonstrated by the few cases in 1986 in the face of the large number of tests (see chapter 5, e.g. figure 5.1). Apparently the trend is largely independent of both the numbers of tests done and the increasing range of tests offered.

What effect might incomplete data have on the five major findings noted in the first paragraph? The incidence of disease would be underestimated due to an incomplete case-list (human error and cases not reported to the Communicable Disease (Scotland) Unit) and the lack of clinical information on a few patients whose laboratory results were compatible with Legionnaires' Disease (see appendix 5). As these errors would not be systematic over time neither the seasonal pattern nor the annual fluctuation is satisfactorily explained in this

way. However, spatial distribution would potentially be sensitive to missing data. The failure to test for Legionnaires' Disease, report diagnosed cases, or provide clinical and other details could reflect attitudes and working practices of doctors in certain geographical areas, and lead to apparent geographical variation. This matter is considered in detail in the next chapter. Lastly, missing cases could cause underestimation of disease clustering.

If no history of travel abroad was obtained from the laboratory request forms, during phone calls between Dr R J Fallon and hospital staff, in communication with consultants and general practitioners in this study,and on replies to the patient questionnaire, the assumption was made that the patient had not travelled during the incubation period. If this assumption was incorrect then travel-related cases would be erroneously placed in the non-travel group, and hence spatial clustering in the "non-travel" group would be reduced (travel-associated cases were less likely to cluster).

The retrospective design of this study had both advantages and disadvantages. The advantages were these: the hypothesis of spatial clustering could not itself bias the diagnosis of Legionnaires' Disease (as might happen in future when the results of this research

are more widely known), and the numbers of cases available for study was approximately known.

The disadvantages were that some data, particularly postcodes, were hard to collect and a few remained missing, many patients could not be contacted, and detailed information about the patient's environment could not be collected retrospectively.

The following chapter presents studies which examined the above and other possible causes of artefact, but focusses on the explanation that geographical differences in the approach to diagnosis underly the variation in disease incidence.

CHAPTER 5

EXPLANATION 1:ARTEFACT

INTRODUCTION

The variation in the incidence of Legionnaires' Disease could be an artefact due to one or more of the reasons in table 5.1. Case listings can be incomplete because of diagnostic inaccuracy and human errors during their compilation. However such errors are more likely to be random than systematic and hence are unlikely to explain consistent variations. As mentioned in Chapter 4 several cases were on one or other, but not on both of the case lists at the Communicable Diseases (Scotland) Unit and the Ruchill Hospital Laboratory.

A serious error would arise if information about cases was unavailable from certain parts of the country e.g. if some laboratories did not use the reference facilities at Ruchill Hospital and did not report cases to the Communicable Disease (Scotland) Unit. Hence, a survey of laboratories' diagnostic practices was done.

Inaccuracy in the data from laboratory forms would not, of itself, nullify observed variation but it would make interpretation of the results more difficult. For example, if information on travel history was incomplete then were the variations in incidence rates for travel and non-travel cases valid? If not, were the variations under or overestimated ? Knowledge of the extent of error in the data set would help in its interpretation.

TABLE 5.1

SOME PLAUSIBLE CAUSES OF ARTEFACT AND APPROACHES TO THEIR ASSESSMENT

Causes of artefact	Investigation done
1. The case listings were incomplete	Ruchill Hospital and Communicable Disease Unit listings were cross-checked (see chapter 4) The laboratory survey studied whether positive specimens were sent to Ruchill Hospital
2. The data obtained from laboratory forms (relating to address, clinical information, travel history and date of onset) were flawed	Corroborative evidence from independent sources was sought and the likely error measured (principally from patients' survey and obtaining physicians' views on the diagnosis)
3. The incidence varied due to variation in	
a. hospitalisation for pneumonia	a. comparison of hospitalisation rates for other respiratory diseases (Chapter 6)
b. availability of diagnostic facilities	b. survey of laboratories facilities in Scotland
c. readiness to do appropriate tests	c. numbers of serology tests related to number of L D and pneumonia cases consultants' attitudes towards diagnosis assessed

Surveys of a subset of patients and the opinions of consultants and general practitioners on the diagnosis, provided information to help assess the validity of the data and results.

If local laboratory facilities were not available there might be inhibition about requesting tests while easy availability of facilities might mean that unnecessary tests get done. Another possibility is that some laboratories might routinely test or actively promote testing for Legionnaires' Disease in cases of pneumonia. Again, information about these aspects was obtained from a survey of laboratory practices

The most important artefact, and hence the major focus of this chapter, is that which would result from geographical differences in testing for Legionnaires' Disease. As many cases of Legionnaires Disease are probably undiagnosed, the reported incidence must be related to the readiness of clinicians to do tests. Whether patients with chest infections or pneumonia are tested for Legionnaires' Disease depends on, a) the likelihood of hospitalisation (this is considered in Chapter 6), b) availability of diagnostic facilities, c) the clinicians' knowledge of, attitudes to and experience of the disease and d) the enthusiasm and guidance of the laboratory consultant. If patients admitted to certain hospitals were tested for Legionnaires' Disease only when

suspicion was high on clinical or epidemiological grounds then, within the catchment areas of these hospitals there might be a low detected incidence of Legionnaires' Disease. The ratio of tests done to diagnoses made would be low as would the ratio of tests done to pneumonia admissions. If tests for Legionnaires' Disease were done on a low threshold of suspicion (e.g. routinely for all pneumonias) then we would predict a high ratio of tests to cases and a high ratio of tests to pneumonia admissions. (The interpretation of these ratios is discussed in more detail in the preliminary discussion).

Table 5.1 summarises the nature of the investigations undertaken to assess and, for item 1, minimise the importance of artefact as a cause of variation. Table 5.2 gives the specific objectives and names of the studies done and described in this chapter.

TABLE 5.2

SPECIFIC OBJECTIVES AND NAMES OF THE STUDIES DONE

Objectives	Name of Study and section number for methods
1. To ascertain the approach of Scottish laboratories to the diagnosis, and particularly their use of the reference laboratory at Ruchill Hospital	Laboratories Study (section a)
2. To assess the validity of the data obtained from the laboratory sources for	
(a) diagnostic information	a) diagnosis validation study: general practitioners' and consultants' opinion (section b)
(b) address, travel history and date of onset	(b) questionnaire to patients (section c)
3. To see whether the variation could be explained on the basis of differential thresholds for testing for legionellosis	(a) differential testing study (section d) (b) consultants' questionnaire (section b) (c) laboratories study: approach to "pneumonia specimens" (section a and d)

METHODS

a. Laboratories study

To assess which microbiology laboratories used the reference facilities at Ruchill Hospital Laboratory and to learn of their own diagnostic service a questionnaire was sent to microbiology laboratories in large Scottish hospitals. Information was requested on: the diagnostic tests done locally, the length of time such tests had been offered, whether positive or negative results were confirmed elsewhere and if so the name of the laboratory which confirmed results, and the laboratories' approach to testing specimens from patients with pneumonia. Laboratories which did no tests for Legionnaires' Disease were asked where they sent specimens they received. To assess the role of the laboratory in promoting testing for Legionnaires' Disease the following question was asked, "When sent serum (or other specimens) from patients with a history of pneumonia or chest infection, say for viral titres (or general culture), would you

(i) Carry out (or request) testing for Legionnaires' Disease only if requested on the lab form?

(ii) Carry out (or request) testing for Legionnaires' Disease automatically?

(iii) Use clinical judgement on the individual case?"

Information on the numbers of serology tests done locally was requested from some laboratories.

Data were analysed manually and with the SPSS pc statistical program (Norusis, 1986). A reminder was sent to non-respondents.

b. Diagnosis validation study: consultants', and general practitioners' views and consultants' questionnaire

Corroboration of the diagnosis was sought by asking the opinion of the consultant in charge of the acute episode and that of the general practitioner. The names of consultants and names and addresses of general practitioners were obtained from hospital medical records officers (or uncommonly from laboratory request forms) and they were sent a letter and a computer printout giving identification details of patients, but not laboratory or clinical details.

General practitioners were asked to comment on the validity of the diagnosis, to state whether the patient had travelled or been hospitalised prior to illness and provide information on the occupation of the patient. Lastly, their permission was sought to write to patients.

Consultants were asked their opinion about the diagnosis and to state whether there was any reason why patients should not be contacted.

Without referring to other information, each patient was coded as, "probable case", "unsure", or "probably not" case based on their general practitioners' replies, their consultants' replies, and on the basis of laboratory information already held. The three sets of coding were done at different times to ensure independence. These codes were compared.

In addition consultants were asked about their approach to the diagnosis of Legionnaires' Disease by the following question:
"Which one of these three statements best describes your approach to the investigation of pneumonias:

(a) I request tests for Legionnaires' Disease only if the diagnosis seems likely on clinical or epidemiological grounds

(b) I request tests for Legionnaires' Disease as part of the diagnostic "work-up" of pneumonia on most or all occasions

(c) I request tests for Legionnaires' Disease once other common causes of pneumonia have been excluded."

For simplicity the consultants who ticked (a) or (c) were categorised as "selective" testers and those who ticked (b) were categorised as "unselective" testers. Consultants were categorised by health board and their responses compared.

Data were analysed manually and by the SPSS pc statistical program (Norusis, 1986). One reminder was sent to non-respondents.

c. **Patients' questionnaire study**

A questionnaire was sent to living patients (one exception was made as a spouse expressed the wish to participate on behalf of her dead husband) for whom the permission of the general practitioner was obtained and no objection to an approach to patients was raised by the consultant. The main objective of the questionnaire was to cross-check the data obtained from other sources. The age, address, month and year of onset of illness were listed and patients were asked to complete missing fields and to correct errors. Patients were asked whether they had travelled anywhere or been hospitalised 10 days prior to the illness. Patients who were working at the time of illness were asked to describe their work and to give the work address. (Additional details about workplace were sought but these data are not discussed in this report).

The data were analysed manually and by the SPSS pc statistical program (Norusis, 1986). One reminder was sent to non-respondents.

d **Differential Testing Study: serology**

The Ruchill Hospital laboratory has a hand-written record of the date, laboratory number, name of patient, result and requesting laboratory or clinician for each specimen received. For the years 1978 to 1986 the requests for serology tests for legionnellosis were categorised (manually) by year, month and requesting laboratory. Where known (from the laboratory survey forms and in response to specific written enquiries) the numbers of tests undertaken by laboratories themselves were added to the figures as indicated in the footnotes to table 5.6. The laboratories were then categorised by health board.

The numbers of discharges for pneumonia (first diagnosis) by health board of residence were obtained from unpublished and published reports (Information Services Division, 1979-1985, and unpublished tabulations). The Information Services Division, on request, tabulated the numbers of cases of pneumonia (ICD codes 480 to 486) discharged from acute hospitals for the period 1978 to 1986, by hospital of discharge, sex and age-groups. The number of Legionnaires' Disease serology tests was related to number of pneumonia cases anf Legionnaires' Disease cases by health board and hospital. The number of cases of Legionnaires' Disease was obtained from this study.

The ratios of tests-to-pneumonia and tests-to-Legionnaires' Disease were calculated manually for health boards and selected hospitals. For simplicity only the first figure of the ratio is given e.g. 25:1 is reported as 25. The figures were prepared using the Microsoft Excel spreadsheet and graphics package (Microsoft Corporation, 1987).

RESULTS

a. Laboratories study

Of the 31 microbiology laboratories in major Scottish Hospitals contacted, 27 responded (87%). Of the four non-respondents one had the same consultant in charge, and apparently the same policies, as one of the responding laboratories. In effect three laboratories had unknown policies. One was in each of Greater Glasgow, Lothian and Lanarkshire Health Boards. All three were known to be users of the Ruchill Hospital service. One laboratory, in Glasgow, only handled environmental samples. As shown in table 5.3, 13 did one or more diagnostic tests for Legionnaires' Disease, usually culture or the indirect immunofluorescence antibody test. In Tayside and Grampian Health Boards, which had a comparatively low incidence of disease, the indirect immunofluorescence test had been offered for a number of years. Both submitted positive sera for confirmation to Ruchill Hospital. Only one of the eight Glasgow laboratories (excluding the Ruchill Hospital Laboratory) did serology using the indirect immunofluorescence antibody test.

Only two laboratories, one in Grampian Health Board and one in the Borders Health Board, routinely did legionella serology on specimens from patients with pneumonia (approach ii) but neither health board had a high incidence of Legionnaires Disease. Of the others,

TABLE 5.3

LABORATORY FACILITIES FOR THE DIAGNOSIS OF LEGIONNAIRES' DISEASE IN SCOTLAND

Health Board (number of laboratories)	Tests done locally (13 laboratories)				No tests done locally (14 labs)
(total number of labs)	IFAT	RMAT	DFA	Culture	
1. Greater Glasgow* (8)	1	1		4	4
2. Lothian (5)	2		1	1	3
3. Lanarkshire (1)					1
4. Argyll and Clyde (3)				1	2
5. Tayside (2)	1			1	1
6. Fife (1)					1
7. Ayr and Arran (1)		1			0
8. Forth Valley (1)					1
9. Highland (1)				1	0
10. Grampian (2)	2			1	0
11. Borders (1)					1
12. Dumfries and Galloway (1)				1	0
Column Totals	6	2	1	10	14

* Ruchill Hospital Laboratory excluded

nine took approach (i) i.e. did legionella tests only on request, nine took approach (iii) i.e. used clinical judgement, and five a combination of (i) and (iii) (one laboratory did not complete the question and another did not handle clinical specimens). All 13 laboratories which did their own tests sent positives for confirmation to Ruchill Hospital (one also sent them to England). Negative findings were routinely confirmed by five of 13 laboratories, again, at Ruchill Hospital. The local diagnostic services had been offered for 2 to 4 years at five laboratories and for 5 to 10 years at four laboratories (missing data for the other four). Of the 14 laboratories which did not do tests 12 referred requests directly to the Ruchill Laboratory, and the other two sent them to laboratories which, in turn, referred positives for confirmation to Ruchill Hospital.

b). <u>Diagnosis validation study</u>

Seven patients were late additions to the case-list and were not part of this study. The names of the general practitioners of 85 patients were not obtained. For 130 of the other 364 patients, there was either no response from general practitioners or they did not have the details to allow an opinion (usually because patients had died or moved). Codeable responses were obtained for 52.1% of all patients and 63.8% of patients of GP's written to. This proportion was higher for 377 patients who were, on the basis of the laboratory data, classified as probable cases (54.5%) than the others (40%).

Table 5.4 (a) shows that general practitioners'/

TABLE 5.4

*AGREEMENT ON DIAGNOSIS BASED ON LABORATORY HELD DATA AND THE OPINIONS OF GENERAL PRACTITIONERS AND CONSULTANTS

(a) Laboratory based category	General Practitioners' opinion			
	Probably Case	Unsure	Probably not case	
Probable case	<u>183</u>	7	14	204
Unsure	0	<u>2</u>	1	3
Probably not case	16	8	<u>3</u>	27
	199	17	18	234

(b) Laboratory based category	Consultants' opinion			
	Probably Case	Unsure	Probably not case	
Probable case	<u>171</u>	8	13	192
Unsure	0	<u>2</u>	0	2
Probably not case	15	9	<u>5</u>	29
	186	19	18	223

(c) General practitioners' opinion	Consultants' opinion			
	Probably Case	Unsure	Probably not case	
Probably case	<u>112</u>	2	8	122
Unsure	1	<u>5</u>	1	7
Probably not case	6	4	<u>2</u>	12
	119	11	11	141

* Underlined figures indicate agreement

practitioners' opinions (based on 234 patients) agreed with mine in 80% (188/234) of cases. Agreement was higher where laboratory data indicated a probable diagnosis (89.7%) than for other cases (46.7%). For the final coding , which was based on all available information, and on which the analysis in Chapter 4 was done, agreement was 84% (data not shown).

The names of consultants for 77 patients were unobtainable and for 149 of the other 372 patients there was either no reply or codeable opinion. Codeable responses were obtained for 49.7% of all 449 patients and 59.9% of patients of consultants written to. Again, the proportion of codeable responses was higher for 377 patients who were, on laboratory data, classified as probable cases (51.3%) than the others (41.3%). Table 5.4 (b) shows that the consultants' opinions, available for 223 patients (representing a response rate of 49.7% of all patients and 59.9% of patients whose consultant was identified), agreed with mine in 80% (178/223) of cases (and this was unchanged for the final coding). Agreement was higher when laboratory data indicated a probable diagnosis (89.1%) than for other cases (51.6%). Both consultants' and general practitioners' opinions were available for 141 patients (table 5.4 (c)) and agreement was 84% (119/141).

The name of either, or both, the consultant or the general practitioner was identified for 384 patients and, in total, a codeable opinion from a clinician was obtained for 316 patients, 82.2% of those whose general practitioners and/or clinicians were identified (70% of the total). Of the 133 patients whose diagnostic coding was entirely based on laboratory held data, 106 (79.9%) were in the probable case group and 27 (20.3%) were not. The latter group represents 6% of patients. (The seven late additions of the master case-list were in the probable group.)

The results concerning the approach of consultants to the diagnosis of pneumonia are in section d,ii.

c. **Patients' questionnaire: accuracy of data on address, onset and travel history**

Permission from general practitioners to write to patients was obtained for 187 patients but for twenty this was deemed inappropriate (e.g. some were known to have died), leaving 167. There were 129 replies (77% response). Ninety five percent of the addresses were reported to be correct and with one exception (wrong town) the error was in the street number or street. No errors affected health board of residence. All dates of onset were reported correct to within four weeks.

The history of travel abroad was incorrect in 4 (3%) cases; three patients had travelled abroad but our records stated otherwise and one patient who was coded as travelling abroad stated he had not done so.

Four other patients had travelled during the incubation period but within Scotland. Five patients gave a history of being in or visiting a hospital during the incubation period. (There was no previous record of these facts).

d. **Differential Testing Studies**

i Serology tests

Table 5.5 gives the number of serology tests done in Scotland in relation to the number of cases of

TABLE 5.5

RELATIONSHIP OF SEROLOGY TESTS TO LEGIONNAIRES' DISEASE AND PNEUMONIA IN SCOTLAND, 1978-1986

Year	Number of serology tests	Number of cases of Legionnaires' Disease	Numbers of pneumonia* discharges	Ratio of tests to Legionnaires' Disease	Ratio of tests to Pneumonia
1978	607	18	7132	34	0.09
1979	583	34	7168	17	0.12
1980	1209	28	6259	43	0.20
1981	1571	16	6620	100	0.24
1982	1802	32	7119	57	0.25
1983	2008	47	7139	43	0.28
1984	3485	104	6842	34	0.51
1985**	4366	66	7368	67	0.60
1986	3410	21	7846	171	0.44
TOTAL	19,311	366	63,493	53	0.30

* ICD code 480-486; 1st diagnosis

**This year was unusual in that the outbreak in the Glasgow Royal Infirmary resulted in a large number of requests for tests from this and other Glasgow Hospitals

Legionnaires' Disease and pneumonia. It is apparent that the numbers of tests rose markedly and consistently over the period 1978 to 1986 but the numbers of Legionnaires' cases was variable and this is reflected in the consistent increase in the ratio of tests-to-pneumonia but a greatly fluctuating ratio of tests-to-Legionnaires' Disease. Figure 5.1 and 5.2 show this in graphic form. This is partial evidence that the tests at Ruchill Hospital were highly specific.

Table 5.6 and figure 5.3 show that, as indicated by the tests-to-pneumonia ratio, the tendency to test for Legionnaires' Disease when managing pneumonia was apparently greatest in Greater Glasgow, Borders, Lothian and Lanarkshire Health Boards (rank order). The yield of diagnoses of Legionnaires' Disease as indicated by the tests-to-Legionnaires' Disease ratio (table 5.6 and figure 5.4) was comparatively high in Greater Glasgow but very low in the Borders, low in Lothian and intermediate in Lanarkshire Health Boards. Most health boards which appear to be selective in testing for Legionnaires' Disease (Forth Valley, Tayside, Highland, Grampian, Argyll and Clyde, Fife), as indicated by the low tests-to-pneumonia ratio, had an average or below average yield of cases of Legionnaires' Disease as reflected by the tests-to-Legionnaires' Disease ratio. Only Dumfries and Galloway, and Ayrshire and Arran Health Boards had the combination of a low ratio of tests-to-pneumonia and an

Figure 5.1 Relationship of the annual incidence rate and the tests-to -pneumonia ratio (R.axis).

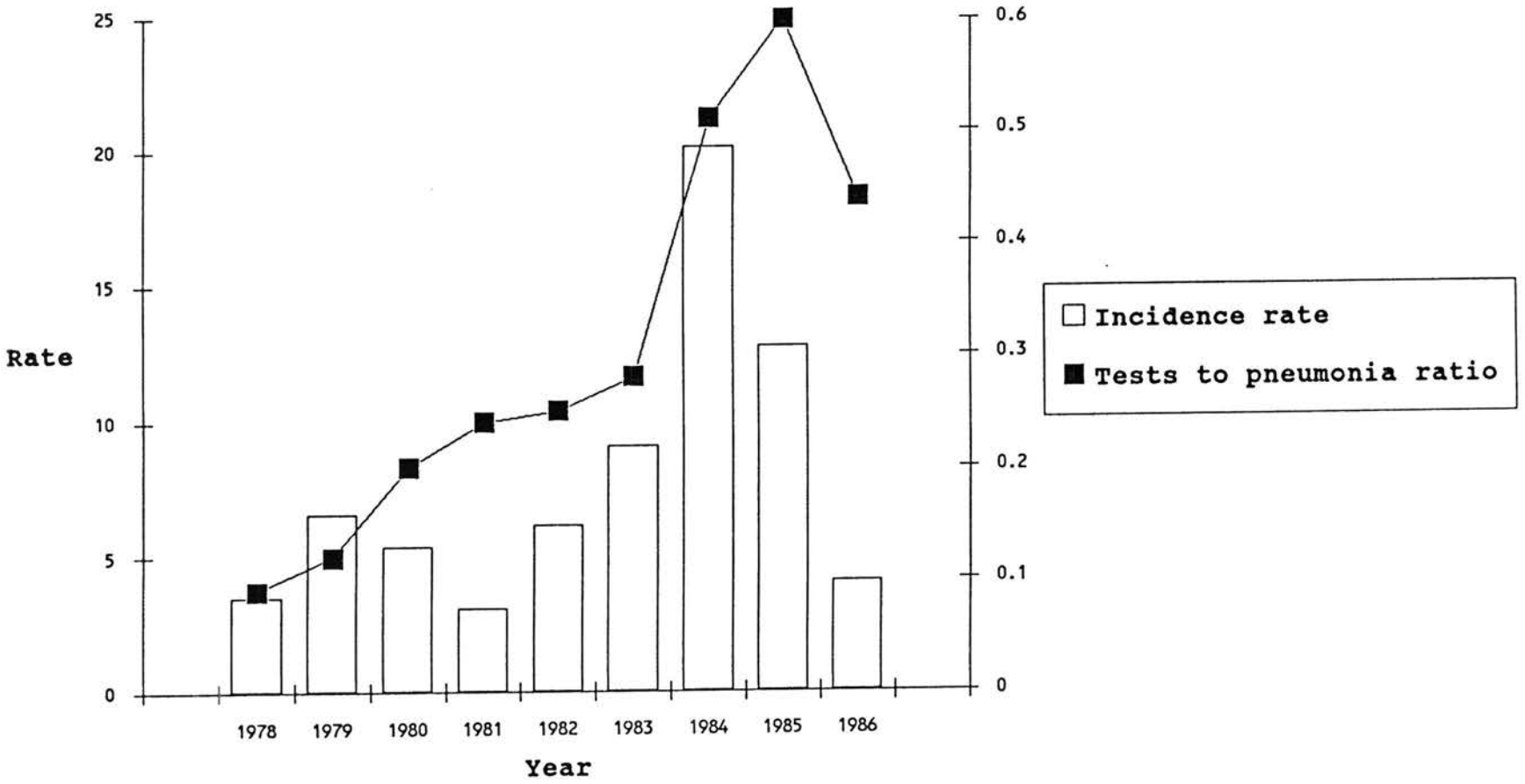


Figure 5.2 Relationship of the annual incidence rate and the tests-to-LD ratio (R. axis).

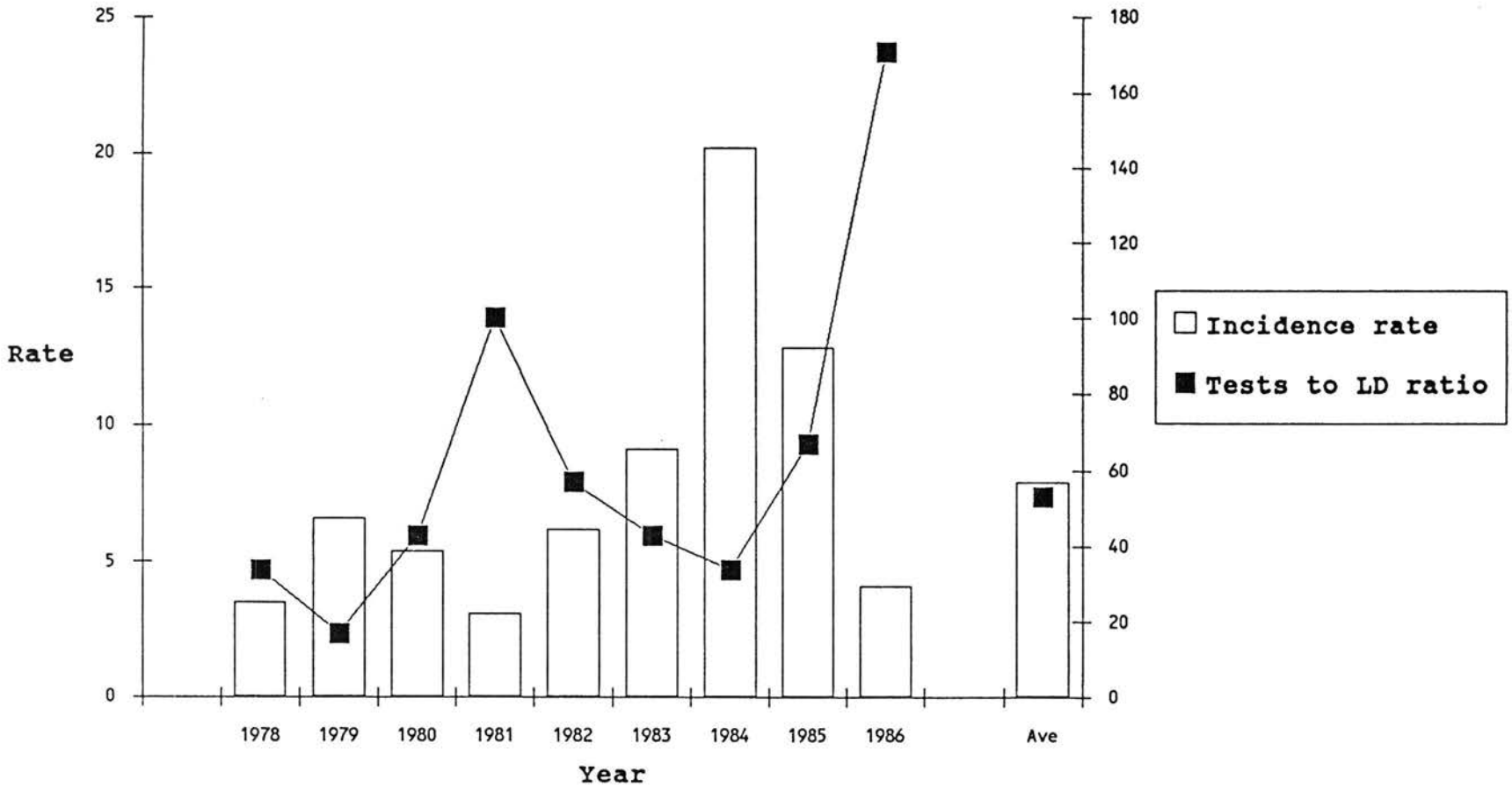


TABLE 5.6

RELATIONSHIP OF SEROLOGY TESTS TO LEGIONNAIRES' DISEASE AND PNEUMONIA BY HEALTH BOARD, 1978-1986

Health Board	Serology Tests	Legionnaires' Disease cases	Pneumonias (1st diagnosis)	Ratio of tests to Legionnaires' Disease	Ratio of tests to pneumonia
Argyll and Clyde	867	12	5,221	72	0.17
Aryshire and Arran	442*	16	4,638	28	0.10
Borders	565	4	1,083	141	0.52
Dumfries and Galloway	189	5	1,511	38	0.13
Fife	658	9	2,785	73	0.24
Forth Valley	471	9	3,072	52	0.15
Greater Glasgow	8,450**	203	15,051	42	0.56
Grampian	406***	6	5,535	68*	0.07
Highland	480	5	1,820	96	0.26
Lanarkshire	1,716	32	5,504	54	0.31
Lothian	3,675**	47	8,888	78	0.41
Orkney +	-	1	260	-	-
Shetland +	-	0	163	-	-
Tayside	966****	14	7,005	69	0.14
Western Isles +	-	1	233	-	-
Totals or averages	18,885++	364	62,769	52	0.30

* Local serology (RMAT); figures include local tests
** Local serology results not included (two laboratories)
*** Underestimate: City hospital serology not included
****Based on Ruchill Hospital data 1978 to 1984 and local laboratory data for 1985 and 1986
\+ Tests diverted to Ruchill Hospital via other laboratories
++ This total does not match the one given in table 5.5 because some tests came from miscellaneous sources which could not be classified by health board e.g. GP's and the CDSU unit.

Figure 5.3 Serology tests per pneumonia discharge (acute intake hospitals, first diagnosis), by health board.

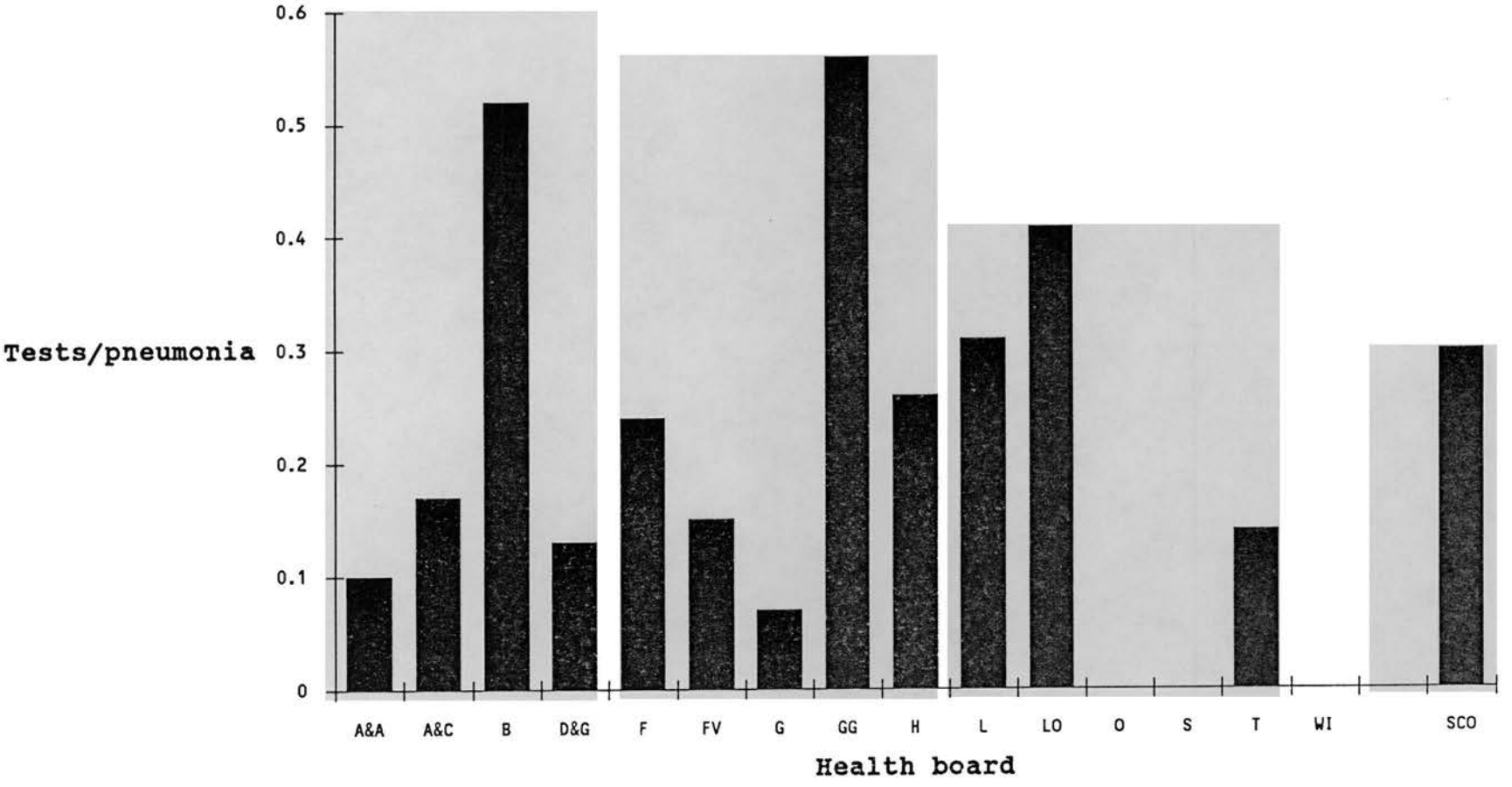
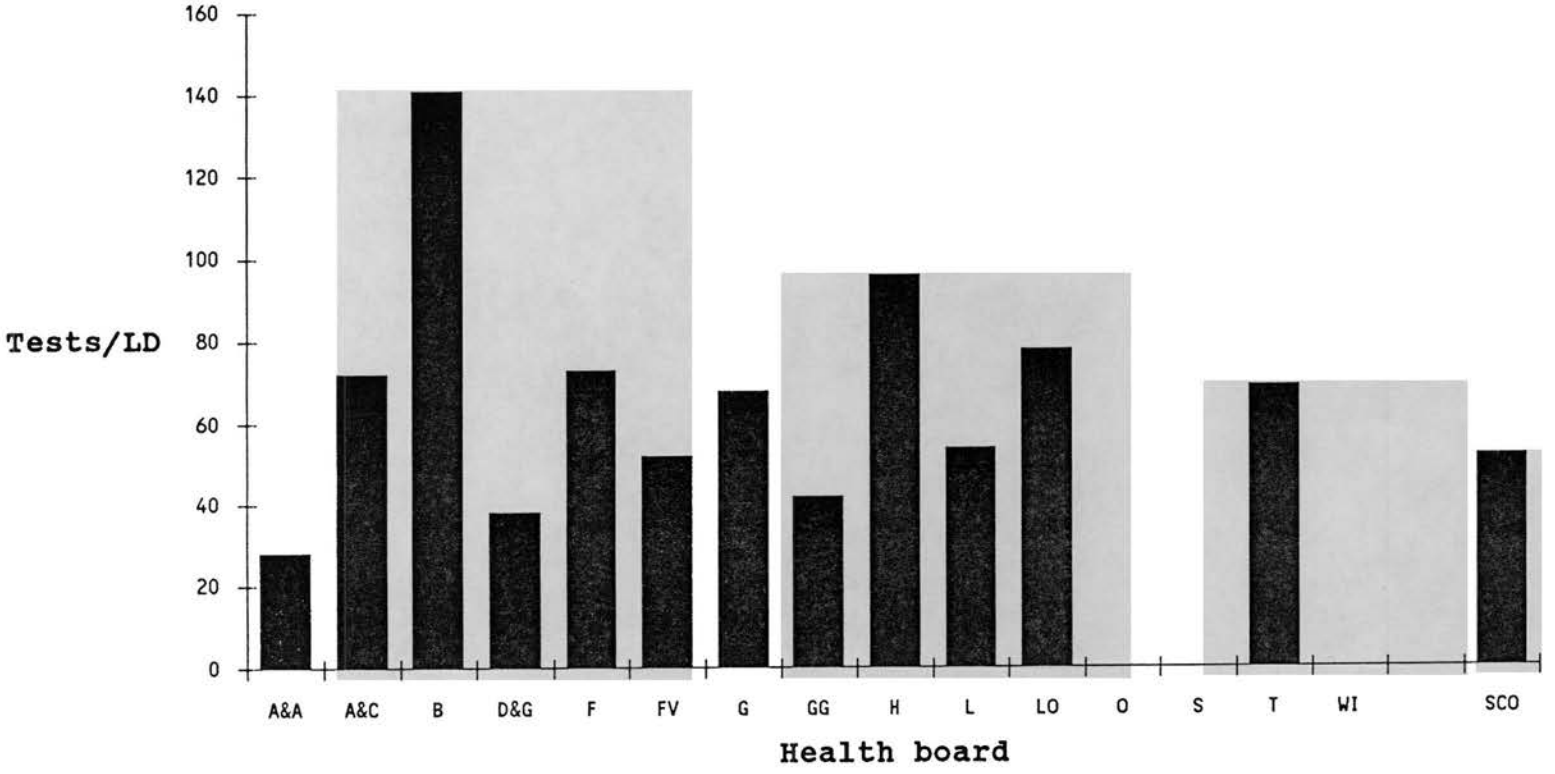


Figure 5.4 Serology tests per diagnosis of Legionnaires' Disease by health board.



above average yield of cases of Legionnaires' Disease in relation to tests done.

Table 5.7 and figure 5.5 examine the time trend in testing for Legionnaires' Disease in Greater Glasgow and Lothian Health Boards. The rise in the annual number of tests done in both boards is striking but similar to the Scottish picture (table 5.5). As the number of pneumonias per year was relatively stable, the tests-to-pneumonia ratio also rose. Prior to 1985 the ratios of tests-to-pneumonias were comparable (0.38 in Greater Glasgow and 0.35 in Lothian) but subsequently in Greater Glasgow the ratio was twice that in Lothian (1.20 compared to 0.62).

The annual variation in the tests-to-Legionnaires` Disease ratio in both health boards was striking (table 5.7 and figure 5.6), supporting the view that the previously demonstrated temporal variation in incidence was real and not an artefact of testing. Overall, despite its higher level of testing, Greater Glasgow had a higher yield of cases per test (one case for 41 tests) than Lothian (one case per 78 tests).

Table 5.8 and figure 5.7 shows the corresponding analyses for the hospitals in the Greater Glasgow Health Board. The tendency to test for Legionnaires` Disease

TABLE 5.7

RELATIONSHIP OF SEROLOGY TESTS TO LEGIONNAIRES' DISEASE AND PNEUMONIA IN GREATER GLASGOW AND LOTHIAN HEALTH BOARDS, BY YEAR

	Greater Glasgow					Lothian Health Board				
Year	Serology Tests	Legionnaires' Disease Cases (N = 203)	Pneumonias (1st Diagnosis)	Ratio of tests to Legionnaires' Disease	Ratio of tests to pneumonia	Serology Tests	Legionnaires' Disease Cases (N = 47)	Pneumonias (1st Diagnosis)	Ratio of tests to Legionnaires' Disease	Ratio of tests to pneumonia
1978	190	12	2,043	16	0.09	95	2	1,002	48	0.09
1979	444	23	1,881	19	0.24	59	2	1,006	30	0.06
1980	528	10	1,550	53	0.34	181	4	913	45	0.20
1981	528	6	1,572	88	0.33	336	1	994	336	0.33
1982	705	8	1,566	88	0.45	432	12	1,038	36	0.42
1983	801	20	1,501	40	0.53	478	18	1,092	27	0.43
1984	1,291	77	1,636	17	0.79	874	3	874	291	1.00
1985	2,422	43	1,631	56	1.48	636	2	974	318	0.63
1986	1,541	4	1,671	385	0.92	584	3	995	195	0.59
Mean per year	938	22.5	1,672	41	0.56	408	5.2	987	78	0.41

Figure 5.5 Serology tests per pneumonia discharge (acute intake hospitals, first diagnosis) in Greater Glasgow and Lothian Health Boards, by year.

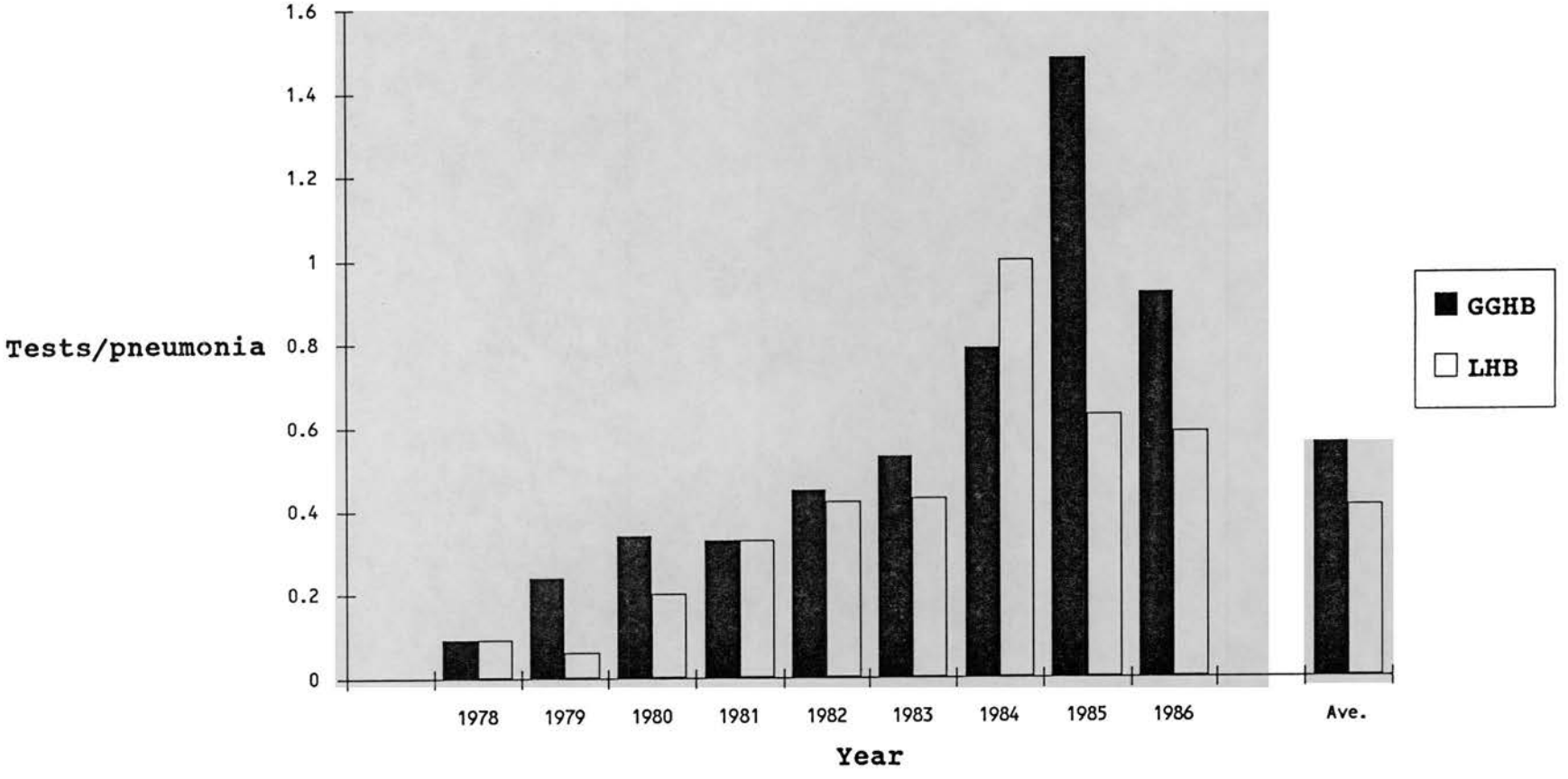


Figure 5.6 Serology tests per diagnosis of Legionnaires' Disease in Greater Glasgow and Lothian Health Boards, by year.

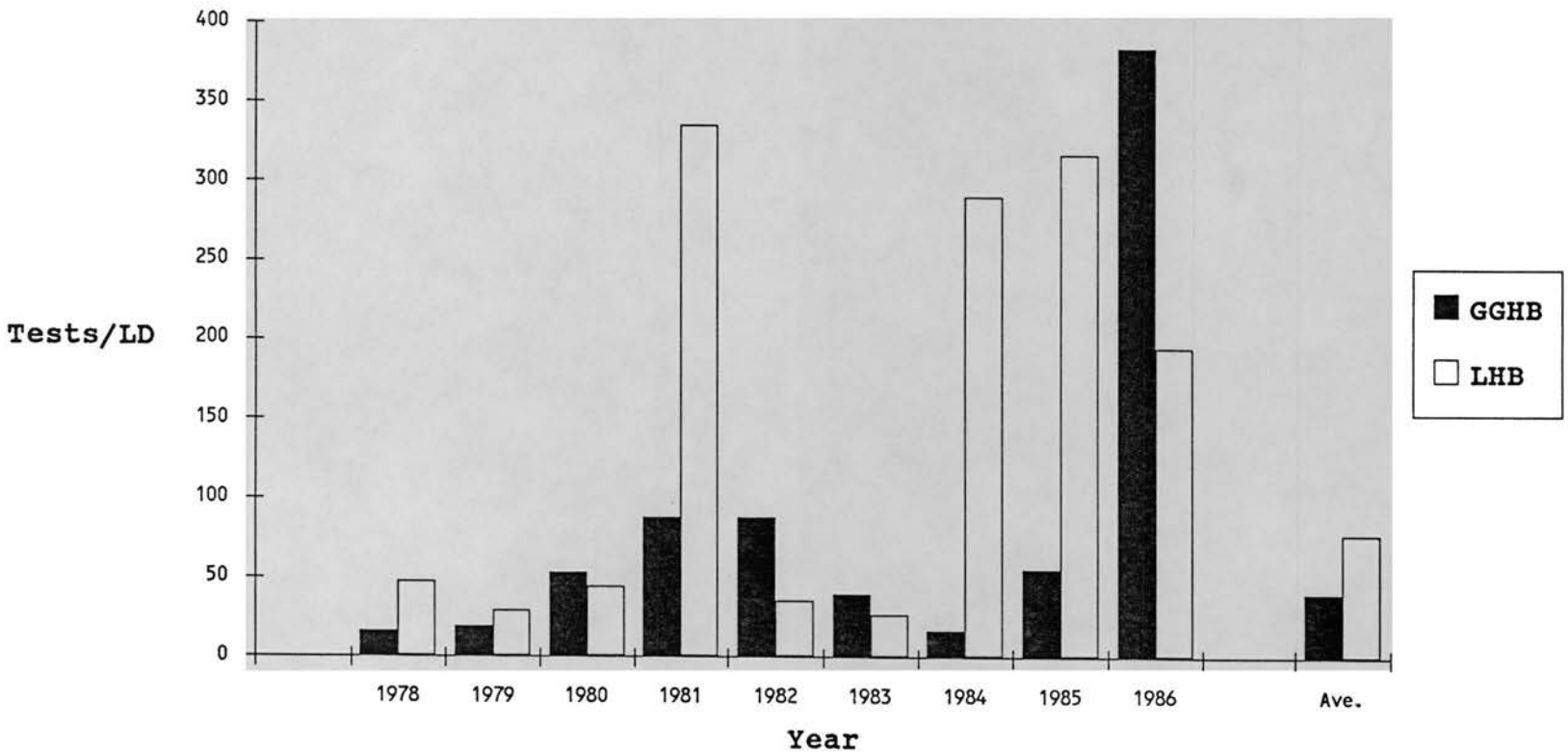


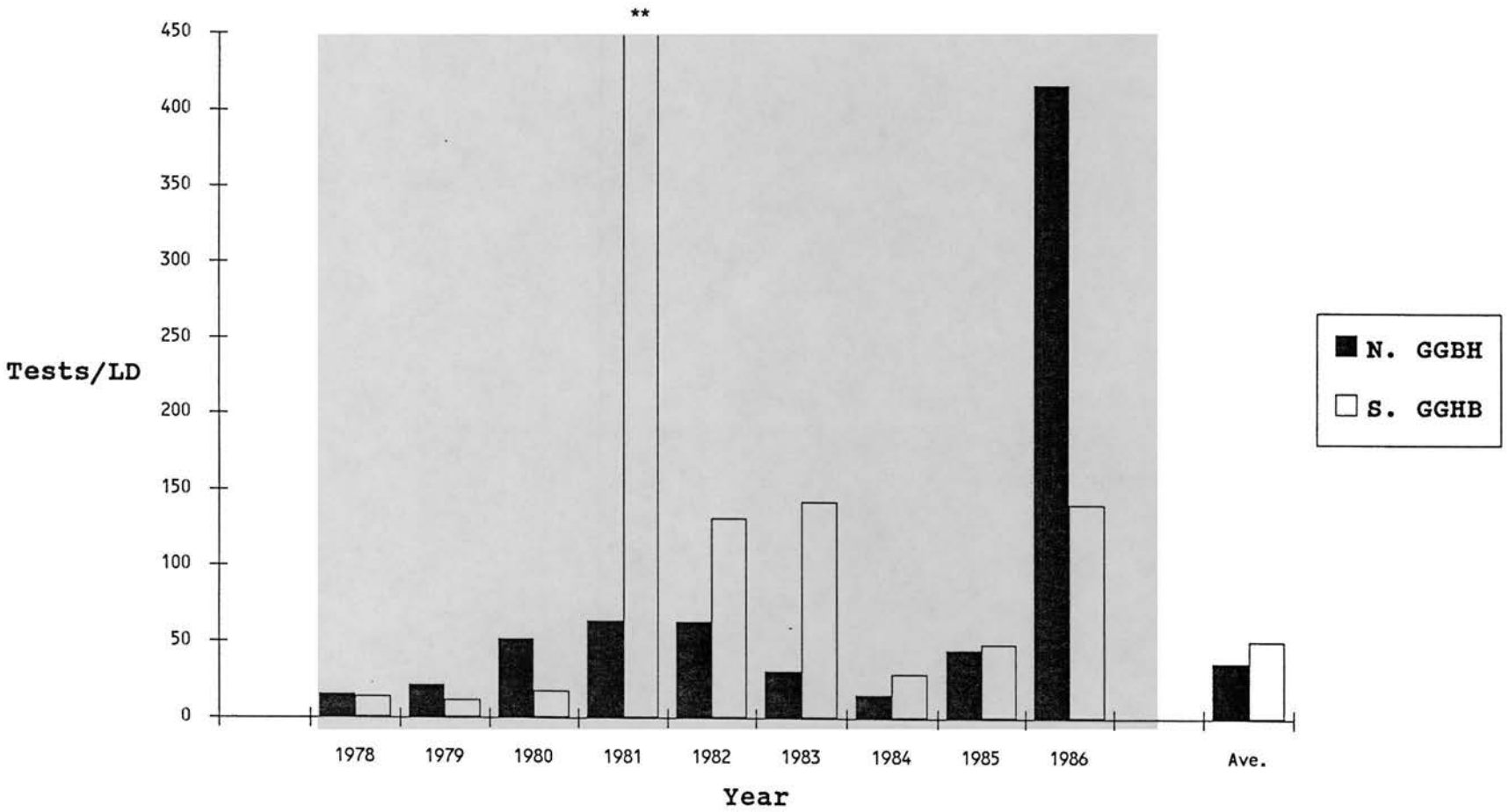
TABLE 5.8

RELATIONSHIP OF SEROLOGY TESTS TO LEGIONNAIRES' DISEASE AND PNEUMONIA IN ACUTE INTAKE HOSPITALS IN GREATER GLASGOW HEALTH BOARD 1978-1986

Hospital	No. of tests	LD cases	Pneumonias	Number of tests per LD case	Number of tests per pneumonia case
Glasgow Royal Infirmary	2,353	74	1,573	32	1.5
Ruchill Hospital	1,644	56	1,621	29	1.0
Stobill Hospital	672	9	1,900	75	0.4
Belvidere Hospital	592	24	1,133	25	0.5
Gartnavel	516	6	1,035	86	0.5
Western Infirmary	832	15	772	55	1.1
Knightswood Hospital	294	5	730	59	0.4
Victoria Infirmary*	371	12	1,402	31	0.3
Southern General*	1,059	16	1,854	66	0.6
North Glasgow	6,904	188	8,764	37	0.8
South Glasgow	1,430	28	3,256	51	0.4
All	8,334	216	12,020	39	0.7

* South Glasgow Hospitals

Figure 5.7 Serology tests per diagnosis of Legionnaires' Disease in N. and S. Glasgow hospitals, by year.



**=Infinity (66 tests/0 cases)

varied from hospital to hospital as indicated by the 5-fold variation in the tests-to-pneumonia ratios for Legionnaires' Disease. Hospitals with high tests-to-pneumonia ratios were in North Glasgow (the Glasgow Royal Infirmary, Ruchill Hospital and the Western Infirmary). The Royal Infirmary and Ruchill hospitals admitted 55% of all cases to Glasgow hospitals. That their diagnostic yield per test was higher than average indicates that they were not testing excessively in relation to their needs. The ratio of tests-to-Legionnaires' Disease varied from hospital to hospital. The Victoria Infirmary had the lowest tests-to-pneumonia ratio and a low tests-to-Legionnaires' Disease ratio, indicating high selectivity in testing. Overall the North Glasgow Hospitals tested at twice the rate of South Glasgow Hospitals but had a higher yield per test (table 5.8).

Table 5.9 and figure 5.7 show the tests-to-Legionnaires' Disease ratios by year for North and South Glasgow Hospitals. Again there was marked annual fluctuation but this was particularly apparent for the South Glasgow Hospitals where, in the three years 1981 to 1983, the diagnostic yield was extremely low (2 cases for 339 tests). The relatively high yield per test in the years 1978 to 1980 suggests that physicians in these hospitals were selective testers. In North Glasgow, the diagnostic yield was relatively consistent until 1985.

TABLE 5.9

RELATIONSHIP OF SEROLOGY TESTS TO NUMBERS OF LEGIONNAIRES' DISEASE CASES DETECTED IN NORTH AND SOUTH GLASGOW HOSPITALS BY YEAR (NUMBERS OF TESTS/CASES).

Year	North Glasgow Hospitals	South Glasgow Hospitals
1978	16 (141/ 9)	14 (42/3)
1979	22 (399/18)	12 (36/3)
1980	52 (468/ 9)	18 (54/3)
1981	64 (447/ 7)	Infinity (66/0)
1982	63 (567/10)	131 (131/1)
1983	31 (647/21)	142 (142/1)
1984	16 (1086/70)	29 (184/5)
1985	45 (1896/42)	49 (493/10)
1986	418 (1253/3)	141 (282/2)
Average (Totals)	37 (6904/188)	51 (1430/28)

Table 5.10 and figure 5.8 provide details on the time trends in testing in Glasgow hospitals. Here, to reduce the effect of different case-mixes, only pneumonias in the age group 15 to 74 were considered. (Also, as numbers were small the ratio of tests to each 100 cases of pneumonia is given). In all hospitals the number of tests increased but the details differ for each hospital. Thus, Ruchill and Belvidere, the two hospitals with infectious disease units, were testing frequently for Legionnaires' Disease by 1978 while the Glasgow Royal Infirmary, which overall had the highest testing rate, did less than average testing for Legionnaires' Disease until 1983.

ii Consultants' approach to the diagnosis

Questionnaires were sent to 167 consultants and 106 (63%) completed questionnaires were received. The response rate from health boards, excepting Tayside, was comparable as shown in table 5.11. Two-thirds of consultants were selective in their approach to the laboratory diagnosis of pneumonia (ticking options i or iii to the question given in the methods, section a). Of the 23 who took an unselective approach (option b) 13 were from the Greater Glasgow Health Board (25% of GGHB respondents), four from Lothian (17% of LHB respondents) and six from other health boards (20% of respondents), notably Ayr and Arran. These differences between the Greater Glasgow, Lothian and all other health boards

TABLE 5.10

ANNUAL NUMBER OF SEROLOGY TESTS DONE PER 100 CASES OF PNEUMONIA (AGE-GROUP 15 TO 74) IN GLASGOW HOSPITALS

	YEAR									
Hospital	1978	1979	1980	1981	1982	1983	1984	1985	1986	Mean
Glasgow Royal Infirmary	4	19	57	51	95	183	300	791	423	214
Ruchill Hospital	48	160	180	192	174	244	270	333	213	202
Stobill Hospital	13	19	70	61	98	46	80	132	118	58
Belvidere Hospital	36	71	117	39	80	165	88	207	- *	100
Gartnavel	6	4	26	101	77	85	105	257	119	87
Western Infirmary	20	47	50	78	108	136	190	357	460	121
Knightswood Hospital	9	25	66	90	63	168	118	229	124	74
Victoria Infirmary **	30	23	41	44	91	69	145	149	79	75
Southern General **	20	11	39	36	133	105	140	421	201	123
North Glasgow	21	64	88	92	104	141	179	362	239	143
South Glasgow	24	17	43	40	120	94	143	320	155	106
ALL	22	52	80	79	107	129	173	353	217	

* The infectious diseases unit in this hospital was transferred to Ruchill Hospital. The mean is based on eight years

** South Glasgow Hospitals

Figure 5.8 Serology tests per 100 discharges of pneumonia (first diagnosis,15-74 years) in N. and S. Glasgow hospitals, by year.

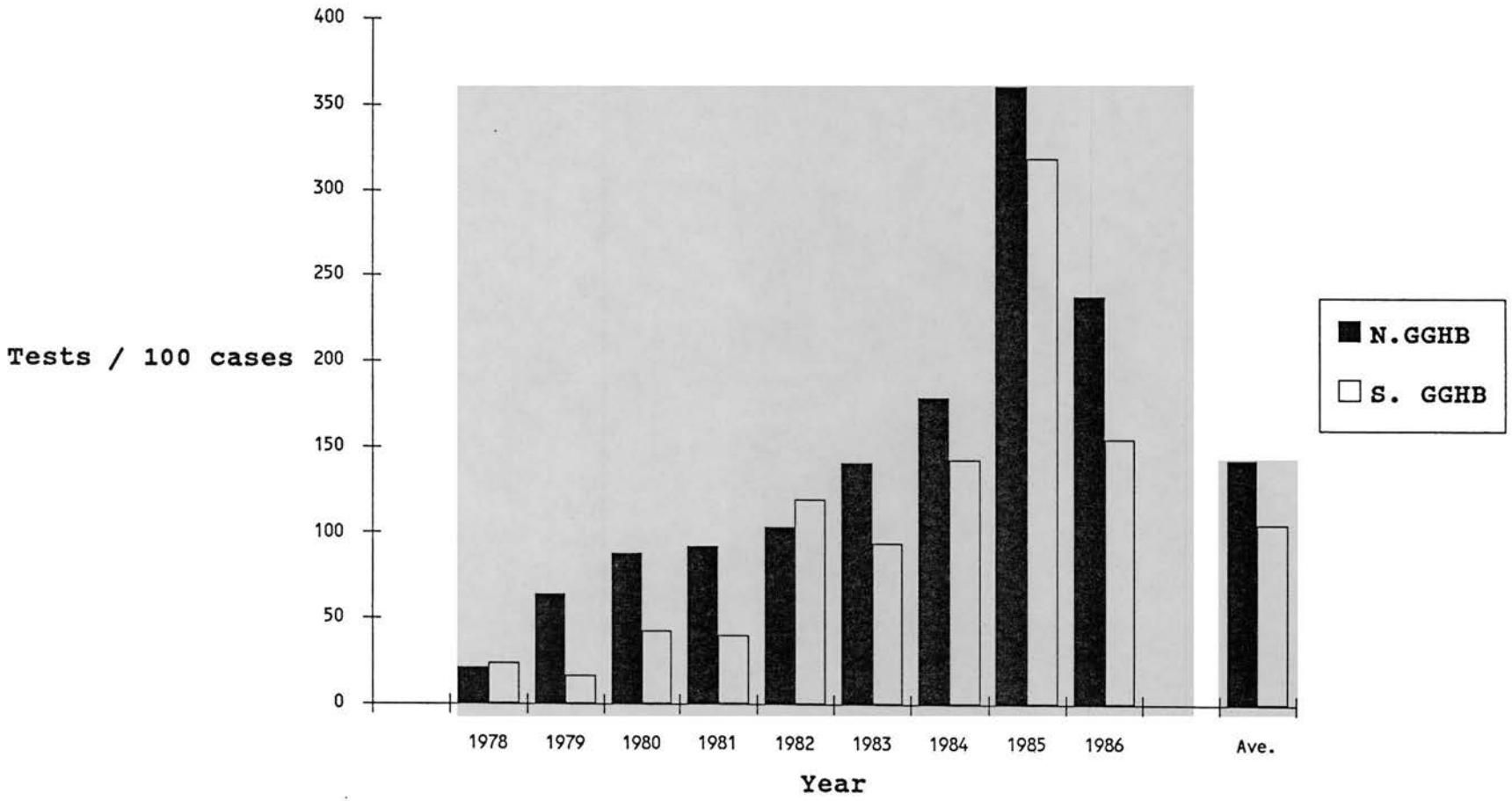


TABLE 5.11

CONSULTANTS' REPORTED APPROACH TO DIAGNOSIS OF LEGIONNAIRES' DISEASE

Health Board (No. of consultants written to)	Usable replies (%)	Selective approach (Row %)	Unselective approach (Row %)
Greater Glasgow (85)	51 (60)	38(75)	13(25)
Lothian (32)	23 (72)	19(83)	4(17)
All other health boards (50 as below)	32 (64)	26(81)	6(20)
Lanarkshire (13)	10 (77)	10	0
Argyll and Clyde (10)	5 (50)	5	0
Tayside (9)	3 (33)	3	0
Fife (4)	3 (75)	3	0
Ayr and Arran (5)	4 (80)	1	3
Forth Valley (4)	3 (75)	2	1
Highland (2)	2 (100)	1	1
Grampian (3)	2 (66)	1	1

(which were not of statistical significance) were consistent with the fact that patients with pneumonia were more likely to be tested for Legionnaires' Disease in Greater Glasgow.

iii Laboratories' approach to the diagnosis

As shown earlier (results, Laboratories study) differing laboratory approaches to the handling of specimens for Legionnaires' Disease did not explain geographical variations in disease. In particular, laboratories which routinely tested specimens from pneumonia patients for legionella antibody were in Grampian and Borders health boards, which both had a low incidence of disease.

PRELIMINARY DISCUSSION

Four potential artefactual causes of geographical variation were examined: differences in laboratory practices; errors in coding the diagnosis; other faults in the data; and differences, among clinicians, in the approach to diagnosis.

Over the last decade several Scottish microbiology laboratories have developed local services for the diagnosis of Legionnaires' Disease but all 27 (of 31) who replied to the questionnaire continued to use the reference laboratory at Ruchill Hospital for corroboration of positive results. The other four were known to be users of the reference service. Hence, it is unlikely that the case-list for 1978-1986 is incomplete due to systematic non-reporting of Legionnaires' Disease cases by some laboratories. Furthermore, the laboratories in health boards with a low incidence of disease did use the reference laboratory. Only eight of the 13 laboratories which did tests locally submitted negative specimens for corroboration to the reference laboratory. If the sensitivity of the methods of these eight laboratories was low compared to the acting reference laboratory then underdiagnosis in the areas served by these laboratories could, theoretically, have occurred.

Comparison of the consultants', general practitioners' and my views (based only on laboratory held data) on the diagnosis showed about 80% agreement overall, about 90% for probable cases but only about 50% for other cases. If the quality of the laboratory held clinical information on the patients whose clinicians (general practitioner or consultant) were identified (85.5% of the total) and did send a codeable reply (82.2% of those written to) was similar to the remaining cases, the diagnostic categorisation seems to have an acceptable degree of validity. It is notable, however, that clinicians were more likely to provide codeable replies for patients classified as probable cases. Possibly, clinicians were more interested in replying or were more able to provide codeable information for these cases. However, most of the patients on whom there was no clinical opinion were, on the basis of laboratory data, coded as probable cases and few (about 6%) were in the other categories.

As some patients with diagnostic serology were categorised as possible cases due to the absence of clinical information (see appendix 5), lack of data probably reduced, not inflated, the case-list.

The patients' questionnaire allowed a check , for a sub-set of cases, on the quality of the data on address at time of illness, age, date of onset, exposure to hospital and travel history. Errors in the former three variables were rare and unimportant. Both exposure to hospital and travel prior to illness were underestimated. Fallon has written that in Scotland a smaller proportion of cases were associated with travel than in England and Wales (Fallon, 1986b). However, this may have resulted

partly from incomplete data. What are the implications of these errors?

If the variation in incidence reflects environmental hazards and not merely unequal exposure to diagnostic tests, then travel-associated cases (and perhaps nosocomial ones) should cluster, by place of residence, weakly or not at all. Incorrect categorisation of travel-associated cases as non-travel cases would result in underestimation of observed variation in incidence by place of residence in the non-travel group. A similar argument would apply to nosocomial cases. However, if unequal exposure to testing for Legionnaires' Disease is the true basis for the variation, then the misclassification by travel and hospital exposure history would have little effect on the observed variation. These issues are discussed again in the final discussion.

The data on differential testing show that the likelihood of being tested for Legionnaires' Disease did vary from place-to-place. Before interpreting the findings, the method needs to be discussed. The indirect immunofluorescence antibody test was the indicator of testing. This decision was justified by the fact that this was the most commonly used test, it was reliable and consistently available throughout the study period. The requests were counted by hospital, and the hospitals grouped by health board. Tests were

not necessarily for patients admitted to the hospital concerned. Hospital laboratories serve surrounding hospitals and general practitioners. Some laboratories route their tests through others e.g. the Legionnaires' Disease specimens from the Western Isles Health Board apparently go to the Highland Health Board. Re-routed requests cannot always be distinguished at the reference laboratory e.g. the Highland Health Board submits specimens with its own covering letter. The assumption was made that such re-routed tests were few. The tests done at the reference laboratory underestimate the Scottish total as some laboratories did their own and did not forward serum from samples tested negative (the figures made available by laboratories were included).

As hospital morbidity records also have errors of completeness and diagnostic validity the ratios of tests-to-pneumonia and Legionnaires' Disease are but crude indicators of the tendency to diagnose Legionnaires' Disease. Because of the flaws in the data sources, a comparison between health boards is probably less valid than a comparison within such an area.

The ratio of tests to disease at a single point in time has limited value; it gives no insight as to why it is high or low. The change in the ratio over time is more valuable. When Legionnaires' Disease occurs local physicians are alerted to the diagnosis and will be more

likely to actively seek cases. In the absence of previous local disease, some physicians might be disinclined to test for this rare diagnosis. A high ratio of tests-to-pneumonia could be a response to a high local incidence of disease and not its cause. In such circumstances the ratio of tests-to-Legionnaires' Disease would be low. If tests were rarely done (say only when the diagnosis seemed probable on clinical and epidemiological grounds) then there would be a low ratio of tests-to-pneumonia and a low ratio of tests-to-Legionnaires' Disease. If there was a high rate of testing, say routinely for pneumonia, then there would be high ratios of tests to both pneumonia and Legionnaires' Disease.

The data for Scotland show a steady rise in the tests-to-pneumonia ratio but a varying tests-to-Legionnaires' Disease ratio and suggest that the annual fluctuations in the number of cases were real and not a result of the varying numbers of tests done. Among health boards the tests-to-pneumonia ratio varied widely (56 tests per 100 pneumonias in Greater Glasgow compared to 14 tests per 100 pneumonias in Tayside). Greater Glasgow's ratio was 108% that of the Borders, 137% that of Lothian and 181% that of Lanarkshire but by comparison the incidence of Legionnaires' Disease was 580%, 298% and 353% respectively (table 4.7). The ratio of tests-to-Legionnaires' Disease in Greater Glasgow (42) was only

Scottish average and lower than in Lanarkshire (55) and Lothian (78). The extremely high tests-to-Legionnaires' Disease ratio in the Borders (141) which had a low incidence of disease, despite routine testing, emphasises that the association between the number of tests done and the number of cases diagnosed is weak.

Greater Glasgow and Lothian Health Boards are comparable in many ways. Their populations are largely urban, they are both centred on major cities, they have much of Scotland's industry and commerce and have comparable health care facilities. They act as regional centres for other health boards and are medical centres of excellence. Both health boards have infectious diseases units. The incidence of non-travel associated Legionnaires' Disease in Greater Glasgow was 3.2 times, and travel-related disease 2.3 times, that in Lothian. Until 1985 the tests-to-pneumonia ratio in Greater Glasgow (0.38) was comparable to Lothian (0.35), and only marginally higher over the whole period (137% of Lothian's). The greater tendency to test was probably a consequence of the high incidence in Greater Glasgow in 1984 and 1985. Indeed, the tests to Legionnaires' Disease ratios were much lower in Glasgow (53% of Lothian's). The steady rise in the number of tests in Greater Glasgow reflects increasing awareness of and frequent diagnosis of the disease. In Lothian, the number of tests rose to a peak in 1984 (the numbers of

cases were maximal in 1983) but then declined, again showing that high numbers of tests can follow a high number of cases.

The incidence of Legionnaires' Disease in Glasgow North of the River Clyde was markedly higher than South of the river. However, the clustering of cases was highest in the G4 and G31 postcodes near to the Glasgow Royal Infirmary and Stobhill Hospitals and in the G12/G11 area near to the Western Infirmary and Gartnavel Hospital. Was this a result of hospitals in the North being more alert to the diagnosis and hence more likely to make a diagnosis in their catchment populations? Table 5.8 showed an overall 5-fold variation in the tests-to-pneumonia ratio in Glasgow hospitals, and a two-fold variation when North Glasgow hospitals were compared to those in the South. Yet, North Glasgow Hospitals had a lower test-to-Legionnaires' Disease ratio, indicating that, in relation to need, they were not testing excessively. Examining the time trend shed further light.

While the tendency to test in the South Glasgow hospitals was comparable in the early years (and the yield of cases per test was higher), in the period 1981 to 1983 only 2 cases were diagnosed but 339 tests were done. Over the same period 38 cases were diagnosed in the North (1661 tests). It is understandable that in

the years to follow, the North Glasgow hospitals cast their diagnostic net wider than the South Glasgow hospitals. The higher yield of cases per diagnostic test despite more testing in the North Glasgow Hospitals is cogent evidence that the clustering of cases was not simply an artefact due to different levels of testing.

Two other perspectives on the issue of differential testing were provided by the data on the laboratories' handling of specimens from pneumonia patients and the consultants' approach to diagnosis. In both cases there was little reason to believe that differential testing could provide the explanation for the variation in incidence.

As artefact does not offer an adequate explanation for the spatial variation the search for real alternatives can begin. The next chapter examines differences in host susceptibility as the explanation. (Variation in hospitalisation is also considered).

CHAPTER 6

EXPLANATION 2: HOSPITAL ADMISSION AND HOST SUSCEPTIBILITY

INTRODUCTION

Variation in Legionnaires' Disease could reflect differences in hospital provision or, closely related to this, the admission policies of general practitioners and consultants. Variation in host susceptibility due to genetic, nutritional or immunity differences (Smith,1976), might also explain the geographical pattern of disease. Conceivably, those parts of Scotland which have a high incidence of Legionnaires' Disease may have a high prevalence of risk factors such as smoking and immunosuppression.

Studies to directly establish or refute the above explanations would be difficult and expensive, as new data would need to be collected. However, since Legionnaires' Disease cannot be clinically distinguished from other pneumonias, we would expect any variation in hospital facilities and admission policies to be non-specific and to affect all pneumonias and perhaps other diseases. If host susceptibility differs geographically, we would expect other diseases which have similar personal risk factors to show geographical variation too. One indirect method of seeking fundamental differences in the composition of populations and their health status is to examine their socio-economic characteristics (Townsend and Davidson, 1982; Townsend et al, 1988).

This chapter explores the following research questions: is the variation in Legionnaires' Disease specific or is it demonstrable for other respiratory diseases, especially other pneumonias; and, can the variation be explained in terms of differences in the characteristics of the populations at risk?

The specific objectives were:

1. To compare the morbidity and mortality for respiratory disease (including pneumonia) in the Scottish health boards and the Health Districts of the Greater Glasgow Health Board, and,
2. To compare the socioeconomic status of the populations of the Scottish health boards and the Health Districts of the Greater Glasgow Health Board.

METHODS AND SOURCES OF DATA

Published mortality data for pneumonia (ICD Code =480-486), cancer of the trachea, bronchus and lung (ICD code = 162) and bronchitis (ICD code = 490-491) were compared by health board and, within the Greater Glasgow Health Board, by health district (Registrar General, 1982; Registrar General, 1983).

Morbidity analyses were based on published Scottish Hospital In-patient Statistics (Information Services Division (ISD), 1979-1985) and new ad-hoc analyses of this data set (kindly supplied by the Information Services Division). The diseases studied were: all respiratory diseases (ISD Code = 31-32); pneumonia (ISD Code = 321); malignant neoplasm of trachea, bronchus and lung (ISD Code = 101); and bronchitis, chronic and unspecified, and emphysema (ISD Code = 329.0).

Numbers of cases of pneumonia (1st diagnosis) by health board, age-group and sex were obtained from the Information Services Division and converted to rates. The incidence rates for Legionnaires' Disease by health district were based on the data in this study.

Census data were used to assess whether the populations of the Scottish health boards and in the

health districts within Greater Glasgow differed in terms of age, sex, unemployment, housing and access to a car (Registrar General, 1982).

RESULTS

Table 6.1 shows that for Greater Glasgow Health Board the standardised mortality ratios for pneumonia (126), cancer of the trachea, bronchus and lung (139) and bronchitis (116) were higher than average but the excess (excluding Island Health Boards) was small. The standardised mortality ratio for pneumonia in Greater Glasgow (126) was only marginally higher than in Lanarkshire (120), Forth Valley (117) and Tayside (109) Health Boards and moderately higher than in Lothian Health Board (84).

Table 6.2 summarises mortality data from 1981 and 1982 for the five health districts in Greater Glasgow. Again, differences were observed but were small. While the N. East District generally had higher standardised mortality ratios than the Glasgow average, those in the S. West District were comparable.

Tables 6.3 gives morbidity data, based on hospital discharges and deaths in 1981, for all and selected respiratory diseases by health board. For the mainland health boards the variations were small, with the exception of bronchitis. Rates per million for all respiratory disease ranged from 6,899 (Dumfries and Galloway) to 12,319 (Lothian), those for malignant neoplasm of trachea, bronchus and lung ranged from 1,433

TABLE 6.1

STANDARDISED MORTALITY RATIOS FOR SELECTED RESPIRATORY DISEASES BY HEALTH BOARD (SCOTLAND = 100), 1981*

Health Board	Pneumonia ICD 480-486)	Trachea bronchitis and Lung Cancer (ICD 162)	Bronchitis (ICD 490-491)
Argyll and Clyde	89	97	116
Ayrshire and Arran	82	75	116
Borders	84	71	79
Dumfries and Galloway	86	97	55
Fife	91	85	133
Forth Valley	117	98	85
Grampian	93	81	49
Greater Glasgow	126	139	116
Highland	85	72	81
Lanarkshire	120	112	111
Lothian	84	95	110
Orkney	(75)	(55)	(65)
Shetland	(58)	(37)	(48)
Tayside	109	89	83
Western Isles	64	67	(91)

*Rates based on less than 20 deaths are given in brackets

TABLE 6.2

STANDARDISED MORTALITY RATIOS FOR SELECTED RESPIRATORY DISEASES IN THE GREATER GLASGOW HEALTH BOARD BY HEALTH DISTRICT, 1981 1982.

Disease	GGHB	AREA				
		North Glasgow			South Glasgow	
	All	West	North	East	S.East	S.West
1981						
Trachea, bronchus and Lung cancer (ICD 162)	139	140	125	157	124	149
Bronchitis, (ICD 490-491)	116	111	163	110	87	127
Pneumonia (ICD 480-486)	126	137	127	139	94	139
1982						
Trachea, bronchus and Lung cancer (ICD 162)	137	103	154	158	126	158
Bronchitis, (ICD 490-491)	86	68	101	91	82	100
Pneumonia (ICD 480-486)	123	134	147	130	99	111

Data from Registrar General Scotland (1982 and 1983).

TABLE 6.3

HOSPITAL DISCHARGE (AND DEATH) RATES PER MILLION POPULATION FOR ALL AND SELECTED RESPIRATORY DISEASE BY HEALTH BOARD OF RESIDENCE, 1981.

Health Board	All Respiratory Disease	Malignant neoplasm of trachea, bronchus and lung	Pneumonia	Bronchitis, (chronic and unspecified) & emphysema
Argyll and Clyde	7797	1485	1169	672
Ayrshire and Arran	8610	1620	1326	944
Borders	9296	2190	1035	846
Dumfries and Galloway	6899	1463	1109	416
Fife	7913	1940	855	826
Forth Valley	7860	1564	1095	385
Grampian	8364	1516	1217	493
Greater Glasgow	11392	2574	1569	967
Highland	8929	1433	1255	719
Lanarkshire	8388	1493	924	684
Lothian	12319	1906	1332	1180
Orkney	6150	1697	1537	106
Shetland	6643	888	541	463
Tayside	11509	1988	1772	1164
Western Isles	7725	1113	818	753

From Information Services Division (Scottish Hospital In-patient Statistics) Edinburgh, Common Services Agency; 1982

(Highland) to 2,574 (Greater Glasgow), those for pneumonia ranged from 855 (Fife) to 1,772 (Tayside), and those for bronchitis ranged from 385 (Forth Valley) to 1180 (Lothian). When the rates in major urban health boards of Greater Glasgow, Lothian, Lanarkshire and Tayside were compared the variations were narrow:

> All respiratory disease rates (per million) ranged from 8388 (Lanarkshire) to 12319 (Lothian);
>
> Neoplasm of trachea, bronchus and lung rates ranged from 1493 (Lanarkshire) to 2574 (Glasgow);
>
> Pneumonia rates ranged from 924 (Lanarkshire) to 1772 (Tayside);
>
> Bronchitis rates ranged from 684 (Lanarkshire) to 1180 (Lothian).

In this group of health boards the higher rate was never more than twice the lower rate. Notably, Greater Glasgow did not rank first for three of the four diagnostic groups. Similar observations were made on other years (data not shown).

The data were re-examined for pneumonia discharges for each sex and by age-group (unpublished, ad-hoc tabulations by Information Services Division; data not shown), but the findings were similar to the above: eg in 1984 for the four health boards above, the highest rate (Greater Glasgow, men 47-74 years) exceeded the lowest rate (Lothian, men 45-74) by 64%. For all other age-groups and for women the margins were narrower.

Table 6.4 shows the discharge rates for respiratory diseases by health district in Greater Glasgow. There is evidence that the statistical returns from the South Eastern District were incomplete (Dr J Womersley, personal communication; Greater Glasgow Health Board), hence the rates from this district were underestimated. Also, the figure for bronchitis in 1985 in the S. West District would appear to be an artefact. Nevertheless, the data support earlier observations made on mortality data ie. that the North East District has a comparatively high discharge rates for respiratory disease. However, even in this district the excess was usually small (the discharge rate for cancer of the trachea, bronchus and lung was 1.7 times the Glasgow average, and for all other conditions the excess was less). By contrast the variation in Legionnaires' Disease was high: for non-outbreak, non-travel related infection the North East District had an incidence about three times the average, (for travel-related infection the S. East District had an incidence 1.7 times the average).

Table 6.5 shows that, in regard to socio-economic indicators of social and material deprivation, which themselves are associated with such risk factors as smoking and disability (Townsend and Davidson, 1982; Townsend et al, 1988), Greater Glasgow ranked high but the variations between health boards were small.

TABLE 6.4

HOSPITAL DISCHARGE (AND DEATH) RATES PER MILLION POPULATION FOR ALL AND SELECTED RESPIRATORY DISEASES IN GREATER GLASGOW HEALTH BOARD BY HEALTH DISTRICT.*

Disease and year	GGHB (number of cases)	Northern Districts			Southern Districts	
		West	North	East	S.E**	S.W
1981						
Cancer of the trachea, bronchus and lung (ICD 162)	792(793)	734	858	1350	385	709
Bronchitis (ICD 490-492)	613(614)	465	1314	618	333	418
Pneumonia (ICD 480-486)	861(708)	872	961	1204	521	804
1985						
Cancer of the trachea, bronchus and lung (ICD 162)	931(902)	810	955	1381	578	1077
Bronchitis (ICD 490-492)	331(321)	220	216	291	205	874***
Pneumonia (ICD 480-486)	936(907)	931	1061	1142	600	1038
1978-1986						
Non-Travel Legionnaires' Disease	161(119)	126	141	363	123	82
Travel-related Legionnaires' Disease	35(35)	34	38	16	61	19

* From unpublished, ad-hoc tabulations prepared on request by the Information Services Division, Edinburgh.

** It is likely that the routine data for this district were incomplete

*** The explanation for this extreme rate is unclear, but it is probably a artefact.

TABLE 6.5

SOME SOCIO-ECONOMIC CHARACTERISTICS OF THE POPULATIONS OF THE SCOTTISH MAINLAND HEALTH BOARDS, 1981 CENSUS
FIGURES ARE PERCENTAGES

Health Board	Population 65-74 yrs	Population 75 yrs+	Unemployment among men (16-64 yrs)	Unemployment among women (16-59 yrs)	Owner occupied housing	Households with more than one person per room	Living in communal establishments	No car in household
Argyll and Clyde	8.4	4.9	16.5*	5.75	30.7*	38.7*	1.3*	54.6*
Ayrshire and Arran	9.0	5.1	16.5*	4.7*	39.3	38.7*	1.3*	54.6*
Borders	14.1	7.4	7.8	3.5	36.4	26.9	1.9	38.4
Dumfries and Galloway	12.8	5.8	10.0	5.1	41.2	26.8	1.6	35.9
Fife	11.7	5.4	10.2	5.5	31.9	32.4	1.4	44.2
Forth Valley	10.9	4.7	12.0	5.8	30.3	32.2	1.6	44.2
Greater Glasgow	9.2	5.4	16.5*	7.4	32.0	38.7*	1.5	54.6*
Highland	11.2	5.4	8.8	5.3	40.8	28.5	2.5	36.0
Lanarkshire	7.0	3.7	16.5*	4.7*	30.7*	38.7*	1.3*	54.6*
Grampian	11.2	5.7	6.8	3.4	40.9	32.8	2.1	38.3
Lothian	11.6	5.6	10.1	4.6	42.4	31.3	1.8	49.5
Tayside	12.7	6.4	11.9	6.6	33.5	33.2	1.9	47.4
Scotland	8.8	5.4	13.0	3.9	34.9	34.7	1.6	48.7

*Strathclyde Region figure: local data not available from published sources.

Table 6.6 shows no major differences between the socio-economic characteristics of the Greater Glasgow Health Board districts north and south of the River Clyde. The North-East District had the highest level of socio-economic deprivation but the South-West District was only marginally better.

TABLE 6.6

SOME SOCIO-ECONOMIC CHARACTERISTICS OF THE HEALTH DISTRICTS OF THE GREATER GLASGOW HEALTH BOARD, 1981 CENSUS. (FIGURES ARE PERCENTAGES)

	Northern Districts		Southern Districts		
Characteristic	West	North	East	S.East	S.West
Population aged 16 to 64 yrs	61	61	60	60	59
Population aged 65 to 74 yrs	19	15	17	18	20
Men aged 75 years or more	1.6	1.4	1.5	1.6	1.7
Women aged 75 years or more	4.2	3.1	3.5	3.9	4.5
Unemployed men	16.1	17.4	26.7	14.3	20.8
Unemployed women	6.5	7.1	10.0	6.0	7.9
Owner-occupied housing	36	29	16	48	24
More than one person per room	15	19	24	14	19
Living in communal establishments	1.3	2.0	2.1	0.6	1.9
No car in household	58	60	78	54	69

PRELIMINARY DISCUSSION

Routinely collected data have limitations; incompleteness and errors of diagnosis for morbidity records and validity of diagnosis for mortality data (Baijal at al, 1989; Greater Glasgow Health board a and b, undated). Further, Scottish hospital morbidity records are based on episodes of care not episodes of illness so do not truly reflect incidence of disease. These faults can give rise to apparent variation and in many instances the real variation is less.

Mortality and morbidity data for respiratory diseases showed small variations particularly between health boards with large urban populations (Greater Glasgow, Lothian, Lanarkshire, Tayside). The variations in the incidence of Legionnaires' Disease were, in contrast, large e.g while the incidence of non-travel Legionnaires' Disease in Greater Glasgow was about three times that in Lothian and 15 times that in Tayside, the corresponding figures for all pneumonia (which include Legionnaires' Disease) were 1.4 and 0.85. The magnitude of variation in the morbidity rates for pneumonia within Scotland was comparable to that of travel-associated Legionnaires' Disease.

Similarly, the variations within the health districts of Greater Glasgow health board were small with the exception of Legionnaires' Disease. The North-East

District had above average mortality and morbidity from respiratory disease, though only marginally more so than the South-West District.

Census data showed that the differences in the socio-economic characteristics between health boards and within the Greater Glasgow Health Board were small, and, in themselves, could not explain the major differences in disease incidence.

The analyses in this chapter show that the spatial variations in Legionnaires' Disease were specific to this diagnosis, and as such both the "host-susceptibility" and "differing hospital admission rates" hypotheses were, effectively, excluded.

The pattern of distribution of Legionnaires' Disease, together with the failure to explain it on the basis of artefact or host-susceptibility, leads logically to the examination of environmental explanations. Foremost of these is the hypothesis that differences in the maintenance and/or location of cooling towers are the basis of the geographical distribution of Legionnaires' Disease. The major alternative hypothesis, that the explanation lies in differences in the quality of public water supplies, or in the location and maintenance of domestic water systems, is less plausible but also requires study. These matters are the basis of chapter 7.

CHAPTER 7

EXPLANATION 3: THE ENVIRONMENT: COOLING TOWERS AND PUBLIC WATER SUPPLIES

INTRODUCTION

To explore properly the relationship between the local incidence of Legionnaires' Disease and the environment would require data on the location, nature and maintenance of water systems known to have been a source of infection, and on the colonisation of such systems by legionellae. Information on the geographical variation in the virulence of microorganisms would also be desirable. Such data are not routinely collected (and such a task would be impractical) and prior to this research, ad-hoc studies of this nature had not been done in Scotland.

The two major known sources of infection, and hence those which merit close study, are cooling towers and domestic water systems. Further, the hypothesis of cooling towers as a source of non-outbreak infection, rather than domestic water systems, is favoured by two earlier epidemiological findings: the abrupt variation in incidence over time in Scotland as a whole and in several health boards, and the striking geographical variation within relatively compact areas. In comparison to cooling towers, domestic water systems would be more uniformly distributed geographically and to pose a continuous rather than episodic risk of infection. Certainly, the abrupt rise and fall in the numbers of cases in cooling tower associated outbreaks is well documented while the epidemic curve in domestic water

system associated disease tends to be more protracted (see also ch 2, section 2, d). In particular, the hypothesis that water sources in private households are a major source of non-outbreak infection, as might be suggested by the study by Stout and colleagues (1987), would not explain the variations in time and space. For these reasons the principle focus of this chapter is on the potential role of cooling towers, and lesser emphasis is given to the public water supply and to domestic water systems.

As discussed earlier (Ch 2,e,ii)evaporative cooling towers provide an ideal environment for legionellae to grow and, indeed, they are frequently grown from cooling towers (Public Health Laboratory Service, 1985a). Cooling towers have been the source of infection for many outbreaks worldwide (Bartlett et al, 1986) and in Britain (Ad hoc Committee, 1986; Committee of Inquiry, 1986; Timbury et al, 1986). Good maintenance of cooling towers has been associated with a lower frequency of contamination with legionellae (Department of Health and Social Security, 1989; paragraph 9) and, recommended maintenance procedures would, by inference, be expected to reduce the risk of disease. Furthermore, whenever outbreaks have been associated with a cooling tower, fundamental principles of maintenance have been breached (see also table 2.6).

Despite the development and circulation of guidelines on cooling tower maintenance (which have been publicised in journals, conferences and the mass-media) outbreaks continue (PHLS, 1989). However, most such guidelines have been directed at National Health Service staff (Department of Health and Social Security, 1980, 1985, 1986, 1987b, 1988). As such, the quality of maintenance, and hence risk of disease, might vary in different types of premises.

Following the Dennistoun outbreak of Legionnaires' Disease (Ad hoc Committee, 1986) the need for addresses of premises with cooling towers became clear, and the Environmental Health Department of the Glasgow District Council started a register. In 1985 a nosocomial outbreak in Glasgow was linked to a cooling tower (Timbury et al, 1986). Circumstantial evidence emerged that sporadic cases of Legionnaires' Disease in Glasgow might be associated with cooling towers (Bhopal and Fallon, 1988). However, there were two limitations of the cooling tower data used by Bhopal and Fallon (1988): firstly that the location of cooling towers remained unvalidated; and secondly, there was no information on the quality of maintenance.

The focus of this chapter is a survey of premises with cooling towers which was done to answer these research questions: was the standard of maintenance of

cooling towers such that a hazard of Legionnaires' Disease from this source exists and might have existed during the period 1978-1986?; and, was there a relationship between the location of cooling towers and location of residence of cases?

With the aim of answering the latter question for other parts of Scotland environmental health departments in local authorities throughout Scotland were written to for details of the number and location of cooling towers in their areas. The results were disappointing, but are included in this chapter to show the difficulties encountered and to present a methodology for analysis of data if it becomes available in the future.

Another research question of relevance was this: could it be that the variation in incidence within the City of Glasgow was due to different water supplies to different parts of the city and hence to the cooling towers? Public water supplies harbour legionnellae (Colbourne 1986, 1988a) and the degree of contamination is influenced by a number of factors including chlorination, pH, and organic and inorganic contaminants. Firstly, information on the public water supply within Glasgow was collated. Secondly, during the cooling tower maintenance study information on maintenance of water in cold water tanks and calorifiers in the surveyed buildings were also collected.

The specific objectives of the studies in this chapter were to:

(1) verify the accuracy of data in the Glasgow District Council register on the location of premises with cooling towers

(2) assess the current maintenance procedures for each cooling tower, particularly to identify poorly maintained towers

(3) discover whether changes in maintenance procedures had occurred, and if so, the reasons for, and nature of, the changes

(4) measure the relationship between the location of cooling towers and the location of residence (and if possible workplace) of cases of Legionnaires' Disease

(5) seek information on the numbers of, and location of, cooling towers in Scottish Local Authorities

(6) collate information on the source and nature of the water supply in the City of Glasgow.

(7) assess the level of maintenance of cold and hot water systems

The underlying aim was support or refute the hyothesis that cooling towers were a source of non-outbreak infection, and, if supported to provide direction for the future prevention of Legionnaires' Disease.

ii The Questionnaire

The questionnaire (which was developed by me in collaboration with the Serious Infections Group of the Glasgow Environmental Health Department) assessed whether established maintenance procedures as recommended by the Health and Safety Executive (1987), The Department of Health and Social Security (1980, 1986) and by Bartlett and colleagues (1986), were being followed. Information on the following aspects of cooling towers and their maintenance was collected: address, administrative procedures, structure, function, cleaning programmes and chemicals used. (The survey started in September 1987 and finished in April 1988.)

iii Analysis

Only data relating to operative cooling towers were analysed. Text data were entered onto computer and manipulated with the Dbase III database programme. Numerical data were punched onto an IBM PS2/30 microcomputer and analysed with the SPSS pc statistical package (Norusis 1986). Maintenance Scores were calculated for each cooling tower by giving points for the features listed in Table 7.1.

The Mann-Whitney Test for non-parametric data was used to test for sub-group differences in maintenance

TABLE 7.1

FEATURES INCLUDED IN THE MAINTENANCE SCORE CALCULATION

Feature	Score
1. Water supply is from the mains	1
2. A log book or other record is maintained	1
3. A named person is responsible for maintenance	1
4. There is no serious structural damage to the tower	1
5. The tower is made of non-porous material	1
6. The air intake is by the induced method	1
7. The tower is in continuous operation	1
8. Shutdowns are for 48 hours or less	1
9. When not in use, the tower is drained	1
10. Prior to recommissioning after shutdown the tower is treated	1
11. Drift eliminators are fitted	1
12. Drift does not bypass the tower via faults in the tower body or drift eliminator	1
13. Drift eliminators are cleaned	1
14. Drift eliminators are of nonporous material	1
15. The fillpack is of non-porous material	1
16. There is no air intake near the tower	1
17. Plumbing connections have an air-break	1
18. The tower can be completely drained	1
19. Routine checks for equipment are made	1
20. Total dissolved solids are checked	1
21. Chlorination is done before cleaning towers	1
22. Anti-corrosives are added	
- once a week or more	2
or	
- at least annually	1
23. Anti-scale agents are added	
- once a week or more	2
or	
- at least annually	1
24. Anti fungal agents are added	
- once a week or more	2
or	
- at least annually	1
25. Biocides are added	
- once a week or more	2
or	
- at least annually	1
26. Sludge is removed	
- a continuous process/dispersant	2
or	
- at least annually	1
27. Foaming does not occur	1
28. Anti-legionella agents additional to the above are added	1

scores (Siegel, 1956; Norusis, 1986). When the variable of interest in sub-group analysis was a component of the maintenance score the score was recalculated after excluding that variable e.g. when cooling towers with and without log books were compared, the maintenance score excluded log books. The maximum possible score was 33.

Analysis was done both on all operative towers at a premise and on a sample of one tower from each premise. The results were similar. Generally, the latter analyses are not given in this report but table 7.2 (page 259) indicates the closeness of the two analyses.

Maps of the location of cooling towers were prepared as described in Chapter 4, section 2f. Maps include three premises known to have cooling towers but which did not participate in the survey. The relationship between the location of residence of cases and location of cooling towers in Glasgow City was studied by visual inspection of superimposed maps. Then the following statistical technique was applied (by the statisticians at the Information Services Division, Edinburgh, directed by Mr James Urquart). For each year, 1978-1986, the cooling towers known to exist (using information on the age of towers) were assigned a location based on the map grid reference number. Again, for each year, every enumeration district in Glasgow City was classified according to the distance from its centroid (population

weighted centre) to the nearest existing cooling tower. Effectively, by aggregating enumeration districts, the City of Glasgow could then be divided into those parts lying within a specified distance from a known cooling tower and those parts not within that distance. The distances specified were: > 1 km from nearest tower; ≤ 1 km; ≤ 0.75 kilometres; ≤ 0.5 kilometres and ≤ 0.25 kilometres.

The populations in the enumeration districts were obtained from the 1981 census. For each year, the expected number of cases in every enumeration district was calculated using the actual age and sex-specific disease rates in Glasgow City for that year. Rates used were those for community-acquired, non-travel Legionnaires' Disease cases; travel-related Legionnaires' Disease cases; and lung cancer (ICD = 162) cases. The lung cancer rates were based on the Scottish Morbidity Record file (but based on the number of individual patients admitted, not admission episodes). Then, the actual number of cases and expected number of cases were calculated for each year for groups of enumeration districts, aggregated according to the distances from cooling towers as above. Lastly, totals for 1978-1986 were obtained by summing the annual observed and expected values in each distance category.

The probability of the observed number of cases occuring by chance, given the expected number, was calculated using the Poisson distribution. Point estimates of the relative risk were estimated on the basis of observed/expected ratios in the groups of enumeration districts lying at various distances from cooling towers as shown in table 7.7 (Breslow and Day, 1987: 93). Ninety five per cent confidence intervals were estimated using the methods outlined by Breslow and Day (1987). Accounts of similar approaches by workers at the Information Services Division to the analysis of geographically based data have been published (Carstairs, 1986; Urquart et al, 1988). This analysis was done on the ICL mainframe computer of the Information Services Division.

(b) Location of Cooling Towers in Scotland

The directors of environmental health (or equivalent) throughout Scotland were written to and information on the number and location of cooling towers in their local authority district was requested. One reminder was sent to non respondents. After this survey had commenced, the experience from the Glasgow cooling tower maintenance study indicated that the data on cooling towers held by local authorities were likely to

be erroneous. Hence, the survey data were analysed simply by tabulating the number of cooling towers reported by the incidence rate in each local authority (for details of calculation of incidence rates see Ch 4, methods section d). Maps were not prepared.

(c) Water supplies in the City of Glasgow

Information on the quality, source and distribution of the Glasgow water supply was obtained from published sources (Devenay, undated) and in writing from the Water Department, Strathclyde Regional Council.

(d) Maintenance of hot and cold water systems at premises containing cooling towers

Data on maintenance of hot and cold water systems were collected during the cooling tower survey at premises with cooling towers. Again, completion of the questionnaire by interview was supplemented with visual inspection. Data were collected on the structure and maintenance of the systems, and the temperature of water from cold water tanks, calorifiers and running water was recorded. Where possible the hot water tap most distant to the calorifier was tested.

RESULTS

(a) Maintenance and location of cooling towers in Glasgow

i General

Of 144 premises on the original list 63 had no wet type cooling tower (most of the latter group had air-cooling, others had removed their towers and some premises had been demolished). Five premises, of which three definitely had towers, did not participate in the survey (two had had outbreaks and apparently took stringent precautions). In 76 of 81 premises surveyed (94% response) there were 174 functioning cooling towers (range 1 to 8). Where several towers were at one site their maintenance was usually similar but at one extreme was a premise where one tower was fully treated, another not at all. Access to several towers was physically difficult and the location of some towers was a potential hazard to maintenance personnel.

At fifty four (71%) premises respondents recalled receiving guidelines on cooling tower maintenance, mostly from commercial organisations (48/54 premises) rather than statutory organisations (18/54 premises).

Maintenance procedures had changed in the previous five years at 59% of premises. Publicity associated with the Dennistoun outbreak (20 mentions) (Ad hoc Committee, 1986) was a major spur to changes such as the

chemical treatment of water, cleaning of towers, involvement of water treatment firms, and bacteriological testing.

In 70% (116) of premises bacteriological tests for Legionnellae had been done, though irregularly or on a single occasion in some places. In nine of these cooling towers legionellae had apparently been detected.

Only 27 premises gave estimates of costs of maintenance which ranged from nil to £6,100 per cooling tower (median £660). Most costs were not specific to maintenance procedures to prevent Legionnaires' Disease.

ii Organisational features

Table 7.2 shows the proportion of premises (as indicated by taking one tower from each premise) and all cooling towers with some of the organisational features recommended for the maintenance of cooling towers. At most premises there was a named person in charge of maintenance, routine checks of equipment were done, towers were treated before recommissioning and a log of maintenance procedures was maintained. However, in nearly one half of premises, total dissolved solids were not measured and at two thirds, towers were not drained when out of use.

TABLE 7.2

PROPORTION (%) OF PREMISES AND COOLING TOWERS WITH ORGANISATIONAL ARRANGEMENTS RECOGNISED AS PART OF GOOD MAINTENANCE.

Variable	Premises (n = 76)	Cooling towers (n = 174)
Log book/record of maintenance was kept	74	82
A named person was in charge of maintenance	93	90
Routine check of equipment was done	91	86
Total dissolved solids were measured	53	51
Towers were not out of action for 48 hrs or more	38	42
When not in use the towers were drained	36	37
Before re-commissioning the towers were treated chemically	81	82

iii Structure and function of towers

The age of the towers ranged from a few months to 27 years (median = 7 years). Fifty five percent were supplied directly from mains water, 36% from storage tank water (29% had a second storage tank placed at a height, a break-tank) and 8% from both. Severe rust or other forms of corrosion affected eight towers and some had inoperative components such as autodosing units (in which case dosing was manual). At some premises the exit of the cooling tower drift was to areas where people were working.

Table 7.3 summarises data on structural and functional aspects of towers. Drift control was poor. Although about two thirds of towers had drift eliminators, in 29% of these drift was observed to exit from cracks or other spaces in the body of the tower (only 50% of the towers had drift eliminators which may have been effective). Only three respondents knew the manufacturer's figures for water lost as drift and drift loss had never been measured. For almost 50% of towers a fresh air inlet was visible in the immediate vicinity.

Commonly, respondents did not know about the capacity of the tower (no information was readily available at 61% of premises), whether plumbing had been altered to meet Water Research Centre standards (53%

TABLE 7.3

SOME STRUCTURAL AND FUNCTIONAL ASPECTS OF COOLING TOWERS OF IMPORTANCE IN THE PREVENTION OF LEGIONNAIRES' DISEASE

Variable	Number (%) of towers	
Tower construction (N=173)		
- wood	7	(4)
- steel	102	(59)
- plastic or fibreglass	63	(36)
- two of the above	1	(1)
Drift eliminator was fitted (N=159)	111	(70)
Drift exits only via drift eliminator (N = 109)	77	(71)
Construction of drift eliminators (N=105)		
- wood	10	(10)
- steel	34	(32)
- plastic or fibreglass	60	(57)
- other	1	(1)
Construction of fillpack (N=167)		
- wood	10	(6)
- steel	28	(17)
- plastic or fibreglass	129	(77)
Tower was (N=173)		
- induced draught	73	(42)
- forced draught	100	(58)
Breaktank was present (N=173)	29	(17)
Cooling tower drainage was separated from other drainage by air break (N=174)	168	(97)
Tower could be completely drained (N=173)	118	(75)
No air intake existed in vicinity of discharge point (N=174)	93	(53)

don't know, 7% yes, 40% no) or whether the plumbing met Water Research Centre standards (39% yes, 2% no, 58% don't know) (Water Research Centre, 1988).

iv Chemical and non-chemical maintenance procedures

Table 7.4 shows that most cooling towers received chemical and non-chemical treatment on a routine basis. Numerous commercial agents were in use. Anti-legionella activity was claimed for many of these agents but forty eight towers received additional treatment specifically to help control legionellae; most commonly chlorine (44). Foaming occurred in 25% of towers and was usually ascribed to the maintenance chemicals.

v Maintenance scores

Maintenance scores for the 174 towers, shown in figure 7.1, ranged from 8 to 30 with a mean, median and mode values of 22 (standard deviation = 5.0), 23 and 24 respectively. Table 7.5 shows that lower maintenance scores were associated with the following: no log book; no recall of receiving guidelines; solitary cooling towers; cooling towers on industrial premises; and no change in procedures in the last five years. Maintenance scores were not lower for cooling towers with a named person in charge or those having routine checks.

TABLE 7.4

CHEMICAL AND MECHANICAL CLEANING OF COOLING TOWERS*

Cleaning/treatment method	% of cooling towers treated	% of cooling towers treated, which receive treatment weekly or more
Anticorrosive agent	82	91
Antiscale agent	80	90
Fungicidal agent	76	80
Biocidal agent	84	77
Sludge removal	94	20
Control of total dissolved solids	68	N/A
Chlorination prior to cleaning the towers (N=167)	39	N/A
Drift eliminators cleaned (N=111)	68	N/A

* N = 174 unless otherwise stated

Figure 7.1 Distribution of maintenance scores.

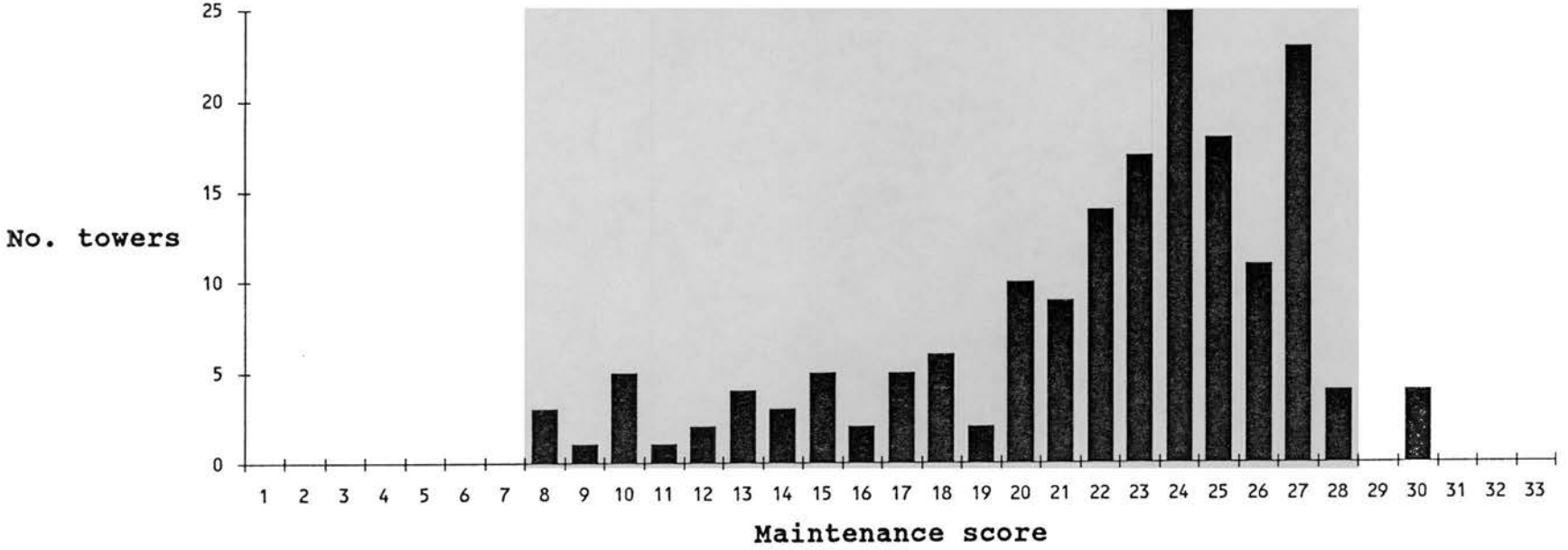


TABLE 7.5

RELATIONSHIP OF MAINTENANCE SCORES TO CHARACTERISTICS OF PREMISES AND COOLING TOWERS

Hypothesis	Categories (N=No of cooling towers)	Maintenance Score and Statistics: Range	Mean	Median	P Value*	P Value for analysis of 76 towers*
1. Where a maintenance log is kept standards will be higher	a. Log book is kept (N=143)	14-29	22.6(3.2)	23.0	<0.001	p<0.001
	b. Log book is not kept (31)	8-24	14.5(4.7)	13.0		
2. Where guidelines have been received the maintenance standards will be higher.	a. Received guidelines (N=139)	8-30	23.3(3.8)	24.0	<0.001	p<0.001
	b. Not received guidelines (N=29)	8-28	14.9(4.6)	14.0		
3. For solitary cooling towers maintenance standards will be lower	a. Solitary cooling tower (N=33)	9-28	20.1(5.3)	22.0	0.007	p=0.045
	b. more than one cooling tower (N=141)	8-30	22.4(4.9)	24.0		
4. Cooling towers on industrial premises have lower maintenance standards than others	a. Hospitals (N=12)	21-30	25.3(2.8)	24.5	<0.001	0.005
	b. Other public buildings (N=40)	11-26	23.0(2.4)	23.0		
	c. Offices (30)	18-30	25.0(2.9)	25.5		
	d. Industrial premises (92)	8-28	20.2(5.8)	21.0		
5. Where procedures have been changed in the last five years maintenance standards will be higher.	a. Procedures have changed (N=113)	8-30	23.3(3.8)	24.0	<0.001	0.007
	b. No change in procedures (N=56)	8-28	19.1(6.1)	20.5		
6. Where a named person has responsibility maintenance standards will be higher	a. Named person (157)	7-29	21.0(4.9)	22.0	0.038	N.S.
	b. No named person (17)	10-27	22.3(6.2)	24.0		
7. Where cooling towers are routinely checked maintenance standards will be higher	a. Routine checks are done (N=150)	7-29	21.3(4.6)	22.0	0.879	N.S.
	b. Routine checks are not done (N=24)	8-27	20.0(6.7)	24.0		

* Based on Mann-Whitney Test

vi Relationship between location of cooling towers and residence of cases

Figure 7.2 shows the location of premises with cooling towers (four years of older) in Glasgow City. Most towers were in or around the city centre or near to the River Clyde. This pattern reflects the location of industry and other large buildings in the City. Figure 7.3 shows the relationship between the location of cooling towers and the location of residence of travel associated Legionnaires' Disease cases. Visually, there is no association. Fig 7.4 shows the relationship between the location of cooling towers and the residence of non-travel, community-acquired cases which were not part of outbreaks. Visually, there is an association and the two patterns are similar. Both cases and cooling towers show the same central clustering. Around several premises clusters of cases can be seen.

Table 7.6 gives the observed and expected number of cases in the groups of enumeration districts located at various distances from cooling towers by travel history. For the non-travel, community-acquired, non-outbreak group more cases were living in enumeration districts near to cooling towers than expected. There was an inverse association between distance of the home from the nearest cooling tower and the observed/expected ratio. A "dose-response" relationship was apparent. By contrast, there

FIGURE 7.2 MAP OF THE LOCATION OF COOLING TOWERS IN THE CITY OF GLASGOW.

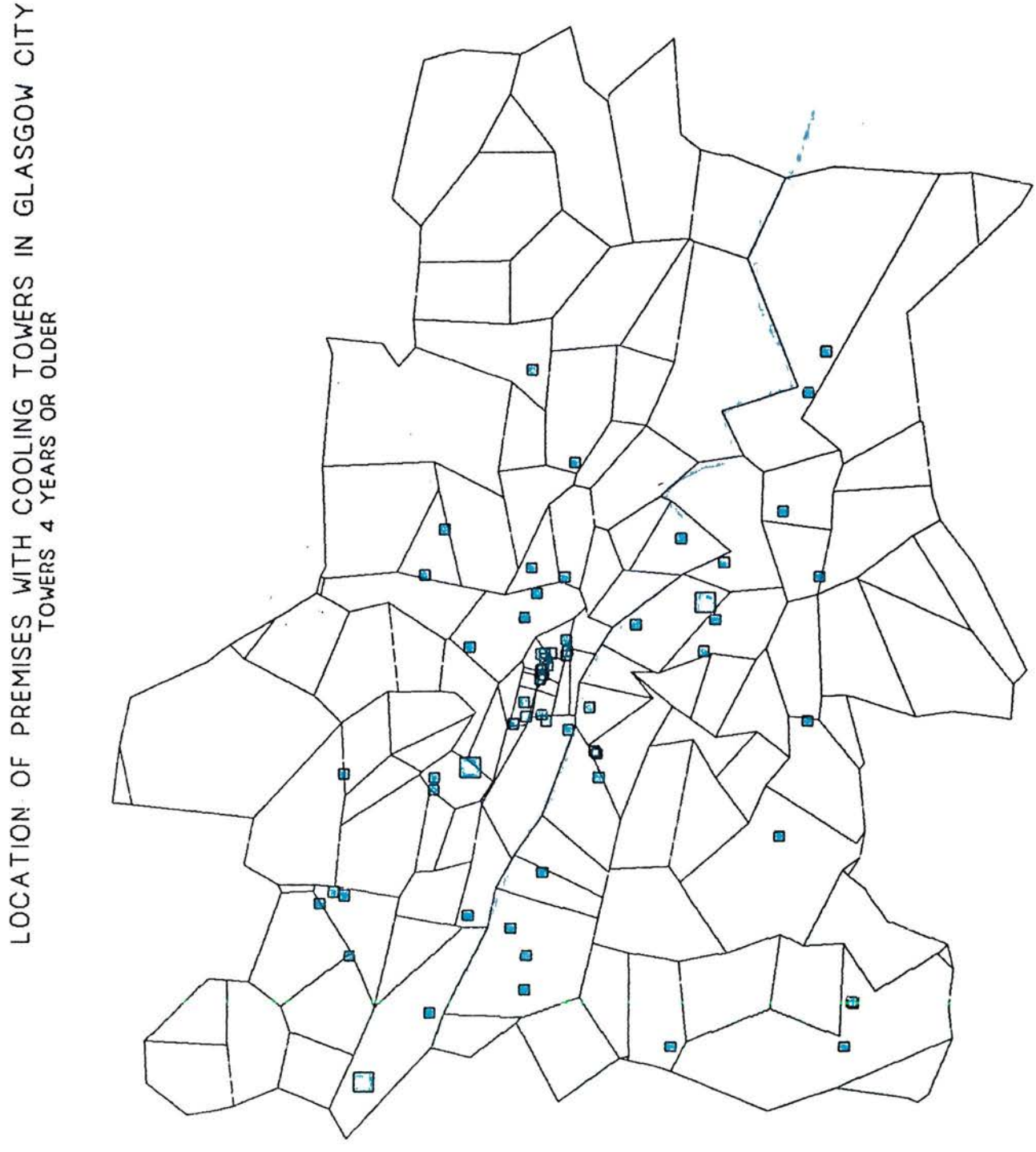


FIGURE 7.3 MAP OF THE LOCATION OF COOLING TOWERS IN THE CITY OF GLASGOW IN RELATION TO THE RESIDENCE OF TRAVEL-RELATED CASES OF LEGIONNAIRES' DISEASE.

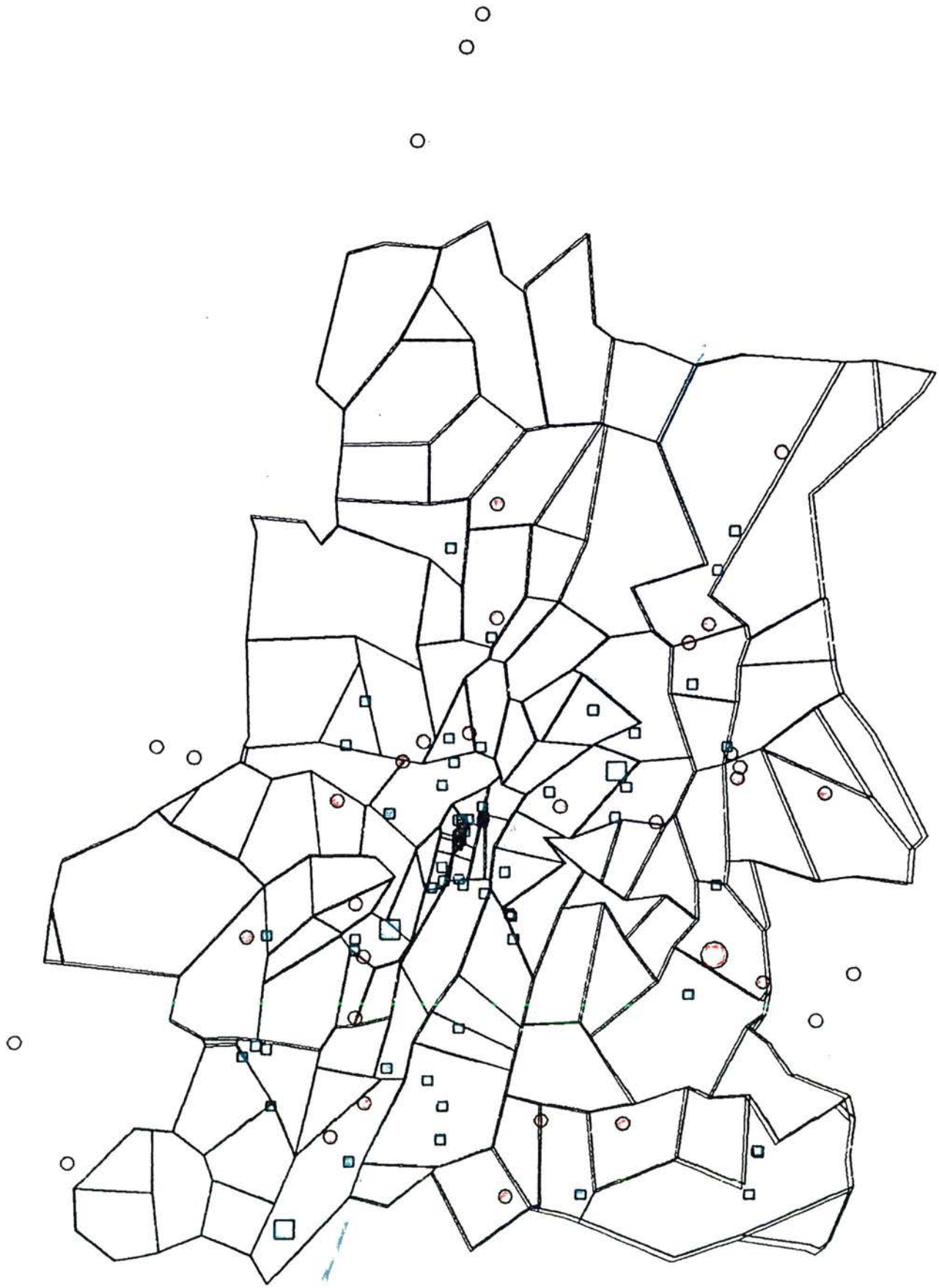


FIGURE 7.4 MAP OF THE LOCATION OF COOLING TOWERS IN THE CITY OF GLASGOW IN RELATION TO THE RESIDENCE OF NON-TRAVEL, COMMUNITY-ACQUIRED, NON-OUTBREAK CASES OF LEGIONNAIRES' DISEASE.

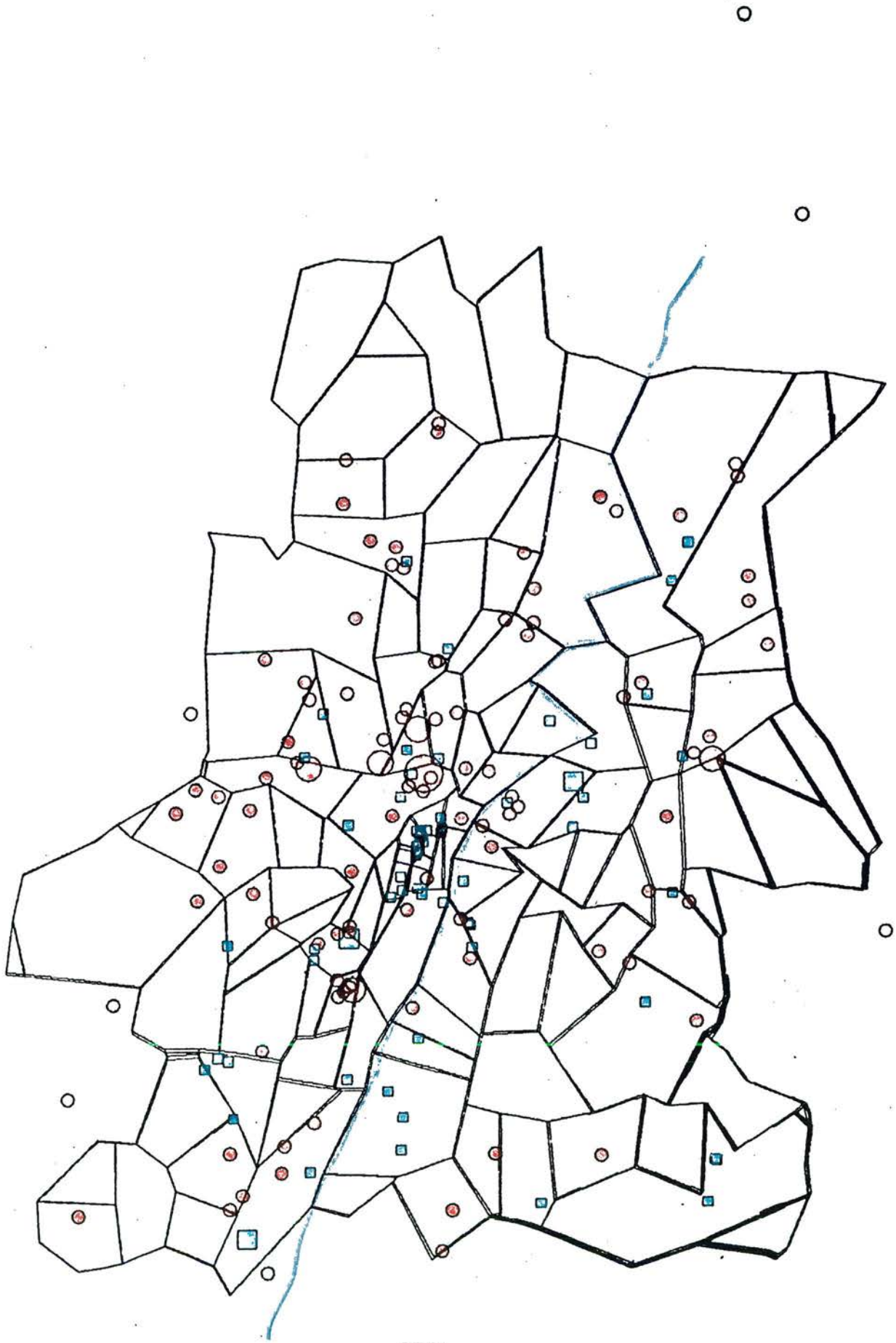


TABLE 7.6

NUMBER OF CASES OF LEGIONNAIRES'DISEASE AND LUNG CANCER, OBSERVED AND EXPECTED, IN RELATION TO THE DISTANCE OF RESIDENCE OF CASES FROM A COOLING TOWER.

Group	Distance of home from nearest cooling tower (kilometres)	Observed cases	Expected cases	Observed/ expected	P value
LD: No travel abroad (N=107)	≤ 0.25	12	4.4	2.73	< 0.001
	≤ 0.5	40	17.5	2.29	< 0.001
	≤ 0.75	55	35.4	1.55	< 0.002
	≤ 1.0	69	53.3	1.29	< 0.022
	> 1.0	38	53.7	0.71	< 0.011
	Any	107	107	1.0	-
LD: Travel-related group (N=27)	≤ 0.25	0	1.0	0.00	N.S.
	≤ 0.5	2	4.1	0.49	N.S.
	≤ 0.75	8	8.4	0.95	N.S.
	≤ 1.0	12	12.7	0.94	N.S.
	> 1	15	14.4	1.04	N.S.
	Any	27	27	1.0	-
Lung cancer (ICD=162) (N=10,159	≤ 0.25	475	407	1.17	-*
	≤ 0.5	1814	1659	1.09	-
	≤ 0.75	3574	3371	1.06	-
	≤ 1.0	5187	5050	1.03	-
	> 1.0	4972	5108	0.97	-
	Any	10159	10159	1.00	-

* Due to the large number of cases, the calculation of the p value using the Poisson Distribution was deemed inappropriate.

was no such relationship for travel-related cases, and in the case of lung cancer, the association was weak. Table 7.7 shows the number of cases observed, expected, and the derived ratio, together with the relative risks for Legionnaires' Disease and lung cancer. The population living within one half of a kilometre of a cooling tower had an incidence rate more than three times that of the population living more than one kilometre away. Again, there was a "dose-response" relationship. No such association was found for travel-related infection but for lung cancer there was a weak association (10-20% excess amongst those living within 0.5 km of a cooling tower).

(b) Location of cooling towers in Scotland.

Of the 55 District Councils written to, 48 replied (87%), but eight of them had no information about cooling towers leaving 40. Of the 40, 11 stated there were no cooling towers in their district. Few of the districts based their responses on systematic surveys but usually on local knowledge. Sometimes estimates were based on the number of air-conditioned buildings rather than on cooling towers. Adding the Glasgow City data left 41 district councils.

No association between the number of cooling towers and the incidence rate was found e.g. of the 23 district councils reporting two or more cooling towers, 9 (39%)

TABLE 7.7

RELATIONSHIP BETWEEN THE DISTANCE OF RESIDENCE OF CASES FROM A COOLING TOWER AND THE INCIDENCE OF LEGIONNAIRES' DISEASE, AND LUNG CANCER

Group	Distance of home* from nearest cooling tower (kilometres)		Cases observed (expected)	Relative risk compared to >1 kilometre group (95% C.I.)
LD: No travel abroad (N=107)		≤ 0.25	12 (4.4)	3.89 (1.92-7.70)
	> 0.25	≤ 0.5	28 (13.2)	3.00 (1.79-5.02)
	> 0.5	≤ 0.75	15 (17.9)	1.19 (0.62-2.22)
	> 0.75	≤ 1.0	14 (17.9)	1.11 (0.57-2.11)
		> 1.0	38 (54.7)	1.0 -
LD: Travel abroad (N=27)		≤ 0.25	0 (1.0)	0.00 (0.9-4.87)
	> 0.25	≤ 0.5	2 (3.1)	0.62 (0.10-2.81)
	> 0.5	≤ 0.75	6 (4.3)	1.33 (0.46-3.66)
	> 0.75	≤ 1.0	14 (4.3)	0.89 (0.25-2.86)
		> 1	15 (14.4)	1.0 -
Lung cancer (ICD=162 N=10,159)		≤ 0.25	475 (407)	1.20 (1.09-1.32)
	> 0.25	≤ 0.5	1339 (1252)	1.10 (1.03-1.17)
	> 0.5	≤ 0.75	1760 (1711)	1.06 (1.00-1.12)
	> 0.75	≤ 1.0	1613 (1679)	0.99 (0.93-1.04)
		> 1.0	4972 (5109)	1.00 -

* The denominator population living within the distance categories varied from year-to-year due to the varying number of cooling towers in each year. The average denominator was as follows: 404,341 lived more than 1km away; 116,339 lived between 0.75 and 1km; 114,886 lived between 0.5 and 0.75 km; 84,466 lived between 0.25 and 0.5km and 27,884 lived less than 0.25km.

had no non-travel, community acquired Legionnaires' Disease compared to 8 of 18 (44%) of the district councils reporting fewer towers (Chi-square = 0.12; df=1; p=0.73).

(c) The public water supply in Glasgow

The water supply for some 95% of the population in the City of Glasgow comes from Loch Katrine which lies North of Glasgow (the water is augmented from Loch Arklet) and is treated at Milngavie waterworks. Chlorine is added to the water (0.5 mg/litre) to leave a residue of 0.1 to 0.25 mg/litre. The residual chlorine level declines as the water moves southwards. The winter chlorine levels are higher than summer. Lime is added to raise the pH from its natural value of approximately 5 to 9.2. (The high pH helps reduce plumbo-solvency.) Other water characteristics of relevance include: conductivity (micro siemens per centimetre) = 42; total hardness (milligrams of calcium carbonate per litre) = 13; free ammonia (milligrams of ammonia per litre of water) = 0.02 or less; iron (micrograms of iron per litre of water) = 53. Appendix 8 holds a full list of the water characteristics.

The only place to receive water from other sources is a strip of land 3½ miles long and ½ mile wide near the South West boundary of Glasgow. Here the water is a mix of Loch Katrine and Balgray reservoir water.

(d) Maintenance of hot and cold water systems at premises containing cooling towers

i Cold water

With one exception cold water tanks were of non-porous materials. Mr G Barr and the survey respondent judged that the location of the tanks at 19% of premises (13/70) would allow the water to warm up in summer. The temperature of the water in the tank (highest recording where several tanks were tested), or in some instances, a nearby cold water tap ranged from 5 to 22° (median = 11°). The temperature distribution was:

5-9°c - 24 premises

10-14°c - 31 premises

15-19°c - 7 premises

20-24°c - 2 premises

Missing data - 12 premises

Lids were fitted on tanks at 87% (61/70) of premises (but about a quarter were inadequate in preventing ingress of dirt). Sludge was removed in 35% (25/72) of tanks, extra chlorination was undertaken in 13% (9/71) water systems, and painting took place in 28% (20/71) of tanks. The use of other chemicals (biocides, antifungal agents etc) was extremely rare (rightly so, as such water is mainly for drinking).

ii Hot water (calorifiers)

The number of calorifiers ranged from one to 45 per premise. At 22% of premises the calorifiers were heated solely by electricity (others by gas and steam). Most premises (55%) had vertical calorifiers and many had convex bases. Cleaning and maintenance programmes at 57% of premises were infrequent (once every 1-2 years) and dictated by insurance requirements, and at 42% of premises there was no routine maintenance at all.

Table 7.8 shows the temperature in or near the calorifier, or at a remote distribution point. While the temperature in the calorifier was high enough to inhibit growth of legionellae in all calorifiers tested, there was a large temperature drop between the calorifier and peripheral taps such that the growth of organisms would be possible in the latter.

TABLE 7.8

TEMPERATURE IN OR NEAR CALORIFIER AND AT A REMOTE DISTRIBUTION POINT

Variable/ temperature	In or near calorifier	At a remote point
a) Summary statistics		
Range (°c)	50-80	18-81
Median (°c)	65	53
b) Temperature recorded by number of premises.		
>55 °c	39	27
50-54 °c	5	16
45-49 °c	0	5
40-44 °c	0	8
<40 °c	0	9
Not known	32	11
c) Temperature drop by number of premises		
0-9 °c	12	
10-19 °c	17	
20-29 °c	6	
30-39 °c	1	
40-49 °c	1	
Not known	37	

PRELIMINARY DISCUSSION

Forty four per cent of the premises on the cooling tower register had no towers. Clearly, to prepare accurate registers a knowledgeable person needs to check towers prior to their registration. Self-administered questionnaires, as previously suggested (Baxter, 1985), probably will not suffice. Possibly, some premises with cooling towers remained unregistered but how can these be found? Large buildings not on the register would need to be checked but this would be particularly difficult because, the presence of a cooling tower would already have been denied. Such valuation was beyond the scope of this study so the degree of underascertainment remains unknown. That many premises on the register had no cooling towers, but plant such as humidifiers, suggests that the methods of ascertainment were diligent. It may be that where cooling towers were badly maintained avoidance of registration was more likely. This hypothesis could not be tested. However, it seems reasonable to assume that the study did not underestimate the quality of maintenance of all Glasgow cooling towers.

Respondents to the cooling tower survey were usually engineers, and many were extremely knowledgeable about cooling towers. Except for the questions on costs, capacity of the towers, drift loss and whether plumbing met Water Research Centre standards (Water Research Centre, 1988), they had little difficulty in providing information. The validity of the answers was not cross-checked (except when possible during the visual inspection) and the true quality of maintenance may have been lower than reported.

Maintenance scores were based on a simple, arbitrary system. Arguably, some features are of greater value

than others e.g. an effective drift eliminator may be of great importance (Miller, 1979; Committee of Inquiry, 1987). However, weighting each factor would also have been arbitrary, and on present knowledge probably unjustifiable. The concept of maintenance scores as indicators of risk and to allow comparative studies, needs further development.

Bacteriological investigation would have been of interest but was not done for reasons of cost, and fear of non-cooperation. Guidelines emphasise that the cooling towers need to be maintained irrespective of whether legionellae are present (Department of Health and Social Security, 1989). The objective in this study was to show whether cooling towers were maintained, not whether they were contaminated.

In a city which has endured two major outbreaks of Legionnaires' Disease (Ad Hoc Committee, 1986; Timbury et al, 1986) and been exposed to intense publicity on the potential hazards of cooling towers (Bhopal, 1986), a high standard of cooling tower maintenance would be expected. Encouragingly, media publicity and other information had led to improvement of maintenance procedures at nearly two-thirds of premises. Some towers were well maintained (though, not surprisingly, none attained the 'gold' standard of a maintenance score of 33), most moderately so, but others were improperly

maintained or neglected. Problems such as severe corrosion, failure to drain cooling towers during shutdown, no chlorination prior to cleaning, foaming of towers, poor drift control and the presence of air intakes close to cooling towers were causes for particular concern (See Ch 2, part 2e and 3c for theoretical discussion).

The greatest compliance with guidelines was in the use of chemicals, perhaps because these are part of general maintenance, and necessary for efficient function. However, most premises remembered receiving commercially produced information from water treatment companies. Such literature emphasises the role of chemicals in the control of legionellae (Dearborn, 1985).

Non-commercial guidelines need wider dissemination and these should emphasise the structural and organisational principles of maintenance, particularly drift control, the use of approved materials, and the proper handling of towers during shutdown. The statistical associations between maintenance scores and certain characteristics of premises can help to decide priorities for information campaigns e.g. start with industrial premises, those without a log book and those where guidelines have not been received.

The relationship between the location of cooling towers in the City of Glasgow and the location of

residence of non-travel, community-acquired cases suggests that cooling towers were a source of infection for non-outbreak cases in addition to the two outbreaks in Glasgow. The visual relationship was confirmed on statistical testing. In the final discussion the interpretation of the relationship between cooling towers and disease is discussed in greater detail.

The attempt to study the relationship between the incidence of disease in local authority districts and the number of cooling towers in such districts was thwarted by the lack of comprehensive, reliable information. A Scottish survey of cooling towers similar to the one done in Glasgow City was beyond the scope of this research programme. The crude analysis of the available data on the incidence of disease and numbers of cooling towers in districts showed no association but proper interpretation of this result is not possible However a method for analysis has been demonstrated should better data become available.

The water supply to Glasgow City was, essentially, from one source and the hypothesis that variation in public water quality results in variation in incidence of disease was untenable. Further, the Glasgow public water supply is known for its purity and does not have the characteristic features of waters which foster legionella growth i.e. river water, warmth, inorganic and

organic deposits, high iron content, stagnation and lack of chlorine (Schofield-and Locci, 1985a; States et al, 1985; Vickers, 1987. The high pH of the water after treatment might be expected to inhibit legionella growth but the pH diminishes as the water enters Glasgow (and was about 7.2 when tested in 1989 in Ruchill Hospital).

The data on the maintenance of domestic water systems has obvious faults but in the absence of other information can be interpreted with caution. Premises with cooling towers are not a representative sample of premises with domestic water systems. The former have an interest in water maintenance arising from their cooling towers. Probably, their domestic water system maintenance is superior to that of most similar premises. As such, the findings were not encouraging. Basic recommended maintenance procedures were followed at few of the premises in the survey. Notably, there was a lack of cleaning and painting of cold water tanks, the temperature in some cold water tanks was around or exceeded 20°c (and would be expected to be higher in mid and late summer), there was a lack of maintenance of calorifiers, and a major differential in the temperature of the hot water in calorifiers and at distant outlets existed.

This chapter has considered environmental explanations for the varying incidence of Legionnaires'

Disease, but using incomplete data sets. Nonetheless there is evidence that, in the City of Glasgow, neither cooling towers nor domestic water systems have been maintained according to guidelines and both sources posed a risk of Legionnaires' Disease. Non-travel associated cases of Legionnaires' Disease were found to be living closer to cooling towers than would be expected by chance and closer than travel-associated cases; strong evidence that cooling towers were a source of infection for such cases.

In the final chapter, the principal findings are reviewed, interpreted and placed in a theoretical perspective. Then recommendations concerning the surveillance and prevention of Legionnaires' Disease (in relation to this work) are made and the potential for future research in this field considered.

CHAPTER 8

CONCLUDING DISCUSSION

(1) INTRODUCTION

The studies upon which this thesis is based have the usual imperfections of the retrospective design, and the cross-sectional survey (as discussed below) but two advantages: the number of cases was large enough for study, and the fact that the hypothesis was unlikely to bias the tendency to diagnose the disease as may happen when the results of this study become known.

The laboratory forms and other records held in the laboratory and at the Communicable Diseases Scotland Unit were usually incomplete in regard to identification, clinical and epidemiological details (for example, see appendix 3). Microbiology laboratories have an important role in the surveillance of infection and particularly in the early detection of outbreaks. For example, the 1984 Glasgow outbreak came to light when Dr. R. J. Fallon noted that of seven patients showing high legionella antibody titres, and all tested on the same day, six lived in the G31 postcode district (Ad-hoc Committee, 1986). The absence of identifying information on the laboratory form, especially date of onset and address, is potentially a major hindrance to the surveillance function of the laboratory.

The data remained less than perfect even after collecting extra information from hospital records, Scottish Hospital Inpatient Statistics records and from clinicians. However, the cross-check on identification and epidemiological details done by the patient survey provided

confidence that the remaining faults would be unlikely to detract from the conclusions. Furthermore, the cross-check of consultants', general practitioners', and my views on the diagnosis, showed high agreement and provided confidence that the case list was not greatly inflated by patients who did not have Legionnaires' Disease.

The response rates to the postal surveys were in line with the past experience of others i.e. 50-70% from clinicians and usually higher from other groups (Cartwright,1978). Checks on the characteristics of non-respondents were not made as the conclusions drawn from each survey alone were not considered to be categorical. For example, the cross-check on diagnosis was based on general practitioners and consultants separately. Again, the differential testing hypothesis was tested in three ways: by examining serology requests, laboratory practices and the approach to diagnosis of consultants who had cared for the patients on the caselist.

The objectives of the study programme were not achieved in two respects. Firstly, the work address and postcode of only a minority of cases was obtained and spatial analysis, beyond point-pattern mapping, was judged to be inappropriate. In retrospect, this problem was to be expected. Many of the Legionnaires' Disease patients contacted had retired or were disabled, and many others were unemployed. Of the rest some had died, moved house and, for others, the permission of general practitioners was not

obtained (usually because of non-response by doctors). The spatial analysis of workplace, place of shopping and place of socialising prior to illness is a future challenge, requiring a prospective study design. Secondly the relationship between the number of cooling towers and the incidence of Legionnaires' Disease could not be studied on a Scotland-wide basis as the quality of the available information on the location of cooling towers was insufficient to allow analysis. Probably, better data will accrue with the increasing interest in cooling tower maintenance following several recent outbreaks (Committee of Inquiry 1986; PHLS, 1988 and 1989) and such a study may become possible in the future.

In this study all cases were due to infections by subgroups of *L. pneumophila* and most were serogroup I. While serological evidence of infection by non-*L.pneumophila* organisms was found in many patients, they were excluded in view of the difficulty in interpreting the results (Taylor, 1987). When the role of serology in diagnosis has been clarified the geographical epidemiology of non-*L. pneumophila* infections will merit study.

Established methods of geographical analysis were used in this study (Nimmo, 1984 and 1989; Carstairs, 1986; Boots and Getis, 1988) but no previous reports of similar analysis of Legionnaires' Disease were found in the literature. Three methodological innovations were developed for these

studies which may merit further development, and application elsewhere. These were:

use of the relationship between the numbers of cases of pneumonia and Legionnaires' Disease, and the numbers of serology tests for Legionnaires' Disease as an indicator of the tendency to test for the disease in relation to local need;

use of travel-related cases as a comparison group when examining geographical patterns;

the development of a cooling tower maintenance score as an indicator of the level of maintenance of a tower.

However, the main contribution of this work has been to undertake a detailed analysis of geographical variation, not only to describe the pattern but to seek to explain it.

The main aim of this chapter is the interpretation of the principal epidemiological findings i.e.

the incidence of Legionnaires' Disease in Scotland was high and fluctuated annually;

there was geographical variation (with, in some places, discrete clusters of cases) in the incidence of Legionnaires' Disease;

the variation was partially but not wholly explained on the basis of geographical differences in rates of testing for the disease and host susceptibility;

the most likely explanation for the variation in Legionnaires' Disease within the City of Glasgow was that cooling towers were the source of infection for

much non-travel disease including, both outbreak and non-outbreak related cases.

The methods and data sources and non-epidemiological findings (e.g. maintenance of cooling towers) have been discussed earlier, but in some instances are briefly discussed again. Sections 2 to 5 present and interpret the principal findings while sections 6 to 8 consider the theoretical and practical issues which arise as a result of this research, and present suggestions for future research.

(2) INCIDENCE IN SCOTLAND

Based on routine reports the mean annual incidence rate in Scotland (9.5 million per year) was about three times that reported from England and Wales and the United States of America (tables 2.2 and 2.3). Following the application of a standard case-definition in this study, the incidence rate in Scotland was 7.9 per million; one of the highest rates reported internationally. Chereshky and colleagues (1986) have reported higher rates than this in New Zealand (10.6 per million based on *L pneumophila* species only). It is noteworthy that both countries, though distant from each other, have a similar population size (and to some extent composition as most of the population is of British descent), climate and health service. The prevalence of antibody in the Scottish population, despite the high incidence, has been low as determined by a number of small studies (Cossar et al, 1982; Fallon and Abraham, 1982b; Timbury et al, 1986), and environmental samples have only

infrequently grown legionellae (Jackson, 1985; Bhopal, 1986).

In Scotland there has been recognition of two major outbreaks of Legionnaires' Disease both in Glasgow (Ad hoc Committee 1986; Timbury et al, 1986), a cluster of cases in Edinburgh in 1987 (Communicable Diseases Scotland Unit, 1987) and a Pontiac Fever outbreak in Lochgoilhead (Goldberg et al, 1988). All except the last were linked with cooling towers.

As the case-definition used was similar to that of others (Centres for Disease Control, 1981 and 1983; Bartlett et al, 1986) the high incidence was not a result of an inflated case-list. Similarly, the diagnostic techniques were comparable (Wilkinson and Brake, 1982; Fallon and Abraham, 1982a; Pastoris et al, 1984).

Whether the comparatively high incidence was due to more case ascertainment by clinicians or a better surveillance system (or both), or reflected a truly higher risk remains unclear. The presence of a central, (acting) reference laboratory providing an accessible service may have promoted an awareness of the disease in Scotland and allowed comparatively good surveillance, particulary as the Communicable Diseases (Scotland) Unit (which is responsible for surveillance) is on the same hospital site. Yet, similar surveillance programmes are organised and maintained with interest in England and Wales (Public Health Laboratory

Service, 1987), the United States of America (Centres for Disease Control, 1988) and other countries. Over the study period, unlike the United States of America, the disease was not notifiable in Britain.

With one exception, Scottish laboratories did not routinely test serology specimens from pneumonia patients for antibodies to Legionnaires' Disease. Similarly, only a small minority of those consultants who had made the diagnosis of Legionnaires' Disease (a sub-group who were more likely to test), undertook diagnostic tests for Legionnaires' Disease on all patients with pneumonias. The average ratio of tests to pneumonia (first diagnosis) was only 0.3 i.e. there was approximately one test for every three cases of pneumonia discharged from Scottish hospitals. Hence, there was little evidence that the high incidence resulted from excessive zeal in testing for Legionnaires' Disease. Table 8.1, shows that in Scotland (and New Zealand) the number of serology tests done per diagnosed case of Legionnaires' Disease was comparatively low and provides some evidence that the observed high incidence in these countries was real. However, in the absence of comparable data on laboratory services and their use, a definitive view of this matter is not possible (no other report of the relationship between the number of tests done and cases was found in the literature).

The incidence of Legionnaires' Disease in Scotland varied markedly from year-to-year and the variation was

TABLE 8.1

RELATIONSHIP OF SEROLOGY TESTS DONE TO LEGIONNAIRES' DISEASE CASES, IN SEVERAL PLACES

Reference	Country	Time	Cases	Tests	Tests: LD Ratio	Comment
Heltberg (1988)	Denmark	1982-1985	32	5,000	156	L pneumophila cases
Chereshky (1986)	N Zealand	1982-1985	130	4,413	34	L pneumophila cases
Woodhead (1986A)	UK*	1979-1984	61	11,490	249	Species not stated
Present study	Scotland	1978-1986	366	19,311	53	L pneumophila cases

* Nottingham area

largely independent of the number of serological tests undertaken. The annual fluctuation was most marked in non-travel related infection and was striking even when outbreak cases were excluded. The annual variation over the same period in published data from England and Wales or the United States of America was unremarkable (see table 2.3); the possibility that variation in time occurred at regional level in these countries but that it was disguised in aggregate data needs study. Unpublished Finnish data show that the number of cases per year varied from 2 in 1981 to 36 in 1983 (data presented at European Working Group on Legionella Infections, 1986 meeting). Local studies, most notably that of Woodhead and colleagues (1986b), also suggest that fluctuations in incidence over time occur. Chereshsky and colleagues (1986) reported figures which show a rising incidence, rather than a fluctuating incidence.

The years 1984 and 1985 in which outbreaks of Legionnaires' Disease occurred in Greater Glasgow were also the years when the largest number of non-outbreak cases (39 in 1984 and 28 in 1985) were observed. The marked decline in 1986, despite a large number of serology tests, confirms that the larger number of non-outbreak cases in earlier years was not simply a result of high awareness.

A high incidence in one part of Scotland was not necessarily associated with a high incidence elsewhere e.g. in 1982 and 1983 the incidence was comparatively high in Lothian Health Board but low in Greater Glasgow. The

positions were reversed in 1984 and 1985. Unknown local, rather than national, conditions apparently determine the risk of Legionnaires' Disease.

These variations in time are powerful evidence against the view that the high incidence in Scotland as a whole, or more locally, results from excessive testing, host susceptibility or vigilant surveillance, but favour the view that differences in the environment, or agent virulence, determine the risk.

Sporadic cases have been associated with outbreaks and may be an early indicator of a change in environmental conditions and hence the risk of outbreaks. Helms and colleagues (1984a) retrospectively searched for cases in Iowa, USA, after an outbreak (1984b) and found a number of sporadic, community-acquired cases which preceded the outbreak. They proposed that where Legionnaires' Disease is endemic the area is at risk of outbreaks. Prior to the Dennistoun outbreak in Glasgow, a number of cases had occurred in an adjoining area of the city, and, in the Glasgow Royal Infirmary outbreak, one case occurred six weeks prior to the main cluster (Timbury et al, 1986). It may be that when environmental conditions allow legionellae to flourish, the risk of Legionnaires' Disease rises and leads to a rise in both sporadic infection, and outbreaks. The investigation of apparently sporadic cases may help prevent outbreaks.

The seasonal peak for non-travel, non-outbreak Legionnaires' Disease in Scotland was in late autumn and early winter; a finding which defies rational explanation but invites speculation (Fallon, 1986b; Bhopal and Fallon, 1988).

Could it be that the peak coincides with the period when cooling towers are cleaned, a time when legionella concentrations are at their highest (Tyndall concent Is there some change in climatology such as wind direction? For example, in summer the prevailing winds are from the north and the air currents low in humidity, but the winter winds are from the west and the air moist (personal communication, Mr. J. Alladyce, principal meteorological officer) which factor would be expected to improve the survival of legionellae in air (Morrow, 1980; Hambleton et al, 1983). Or is it that the conditions which promote legionella growth are acquired late in the year for unknown reasons? Studies to examine the environmental distribution of legionellae at different times, as reported by Bercovier (1986) and Tobiansky (1986), would be of value.

(3) GEOGRAPHICAL VARIATION

Extraordinary geographical differences in both the proportion of pneumonias which are diagnosed as Legionnaires' Disease and prevalence of legionella antibody have been demonstrated but never satisfactorily explained (Anonymous, 1983 and studies in tables 2.2 to 2.5). The variation can be explained partly, but not wholly, on the

basis of differences in diagnostic practices (Anonymous, 1983) and, by inference, the variation indicates either host susceptibility or environmental differences (which remain ill-defined). In this study variation in the incidence of Legionnaires' Disease was observed between health boards, local authorities, cities and between areas within health boards. The high incidence in the Greater Glasgow Health Board, and within certain areas of the City of Glasgow were particularly striking.

There are six important theoretical explanations for geographical variation:

1. The disease varies in time but, on a long term basis, the incidence is geographically similar. If so, spatial variations could result from studying the disease incidence at a point in time. Such an explanation could explain much of the differences observed in many of the short term studies previously described (table 2.4 and 2.5) but not this study of a nine-year period.
2. The geographical variation results from an erroneous data set. This possible explanation has been considered and refuted in Chapter 5 and will not be considered further.
3. The quality and quantity of the tests undertaken at laboratories varied from place to place. This possibility was considered in chapter 5 but will be considered again.

4. The tendency to test for Legionnaires' Disease varied from place-to-place. This, the differential testing hypothesis, is a key one and will be discussed in some detail.

5. Host susceptibility varies. This possibility was discussed in Chapter 6 and found wanting; the main points are reiterated.

6. The variation reflects environmental differences, or differences in virulence of the agent. These possibilities are discussed in section (4).

Over the study period most diagnoses of Legionnaires' Disease were made or confirmed at the acting reference laboratory in Ruchill Hospital, Glasgow. All of the laboratories which responded to the laboratories survey sent their positive results for confirmation to the acting reference laboratory. Some laboratories did not send negative serology for confirmation. If, in their hands, false negative errors were commoner than at the acting reference laboratory, the areas served by such laboratories might show a falsely low incidence. This explanation of the observed variation, though to be borne in mind, is an improbable one.

Use of a service is related to awareness of its existence and ease of access to it. The first cases of Legionnaires' Disease in Scotland occurred in the Greater Glasgow Health Board area (Grist et al, 1979) as did the two major outbreaks of Legionnaires' Disease. Though publicity

was national, Glasgow physicians would undoubtedly be more alert to the diagnosis than others. Glasgow physicians were also physically closest to the reference diagnostic service at Ruchill Hospital. Hence, we would predict a higher utilisation of the diagnostic service and, resulting from this, a higher incidence of disease in Glasgow. However, the facts indicate that this simple and attractive explanation does not adequately explain the variation observed.

While all cases of Legionnaires' Disease in Scotland up to December 1977 were in the Greater Glasgow Health Board, by 1978 there were cases in several health board areas (see table 4.15). The highest annual incidence of non-travel related disease in Scotland up to 1983 was in Lothian Health Board (table 4.15 and corresponding text). However, the data on serology tests done in relation to both pneumonia (discharges from hospital) and Legionnaires' Disease, provide further evidence that greater testing was not a major explanatory factor for the geographical differences.

Greater Glasgow Health Board hospitals requested more serology tests for pneumonia (56 per 100 discharges for pneumonia) than for Scotland as a whole (30 per 100 discharges) but was only marginally more than in comparable health boards such as Lothian (41 per 100 pneumonia discharges). Furthermore, there was evidence that the higher level of testing in Greater Glasgow followed and reflected a higher incidence of disease there. Despite

testing more, the ratio of tests-to-Legionnaires' Disease in Greater Glasgow (42 tests per case diagnosed) was less than the Scottish average (52 tests per case) and substantially less than in Lothian (78 tests per case). Notably, the ratios of tests-to-pneumonia were similar in the Greater Glasgow (38 per 100 cases) and Lothian Health Boards (35 per 100 cases) until 1984, the year of the first outbreak. The ratio of tests-to-Legionnaires' Disease varied greatly from year-to-year, indicating a true annual variation in the incidence, and, furthermore, a variation largely independent of the numbers of tests done. The variation in the incidence of disease within the Greater Glasgow Health Board could not be satisfactorily explained on the basis of different approaches to testing between hospitals. Again, diagnostic practices changed over time reflecting the changing experience of Legionnaires' Disease within hospitals.

The most plausible interpretation of these observations on the ratios of tests-to-pneumonia, and tests-to-Legionnaires' Disease is this: high rates of testing follow, and reflect, a higher frequency of admission of cases. The differential testing hypothesis cannot explain the variations observed; it offers, at best, only a partial explanation.

Could the geographical differences in disease incidence result from differences in host susceptibility? Insofar as susceptibility is related to indicators of socio-economic

status or is reflected in the incidence of other respiratory diseases (carcinoma of the trachea, bronchus and lung; other pneumonias; bronchitis) the answer to the question seems to be yes, but it is likely to be a small part, of the explanation.

The populace of the Greater Glasgow Health Board was the most socially deprived in Scotland and ranked high in terms of mortality and morbidity for a number of respiratory diseases (tables tables 6.1 and 6.3). But, the excess of respiratory diseases, excepting Legionnaires' Disease, was small in comparison to other health boards with urban populations. Interestingly, the incidence of lung cancer in Glasgow and the West of Scotland seems to be disproportionately high in relation to the use of tobacco in comparison with other studies (Gillies et al, 1988).

Within Greater Glasgow Health Board there were small differences, by health district, in socio-economic indicators of deprivation, and morbidity and mortality. Previous work, based on comparison of the morbidity and mortality within 87 neighbourhoods in the Greater Glasgow Health Board showed spatial differences at the small area level but unfortunately the base data were incomplete, and had numerous other flaws (fully discussed by the authors of the reports) including that of not accounting for cross-boundary flow (Greater Glasgow Health Board, undated, a and b). The effect of these errors, particularly the varying degree of completeness of morbidity returns would probably

magnify geographical differences in morbidity. However, the results were interesting in relation to the present work. The greatest degree of spatial variation was for bronchitis and lung cancer. The highest rate for bronchitis was 293, about 3.3 times the average for the health board and the highest rate for lung cancer was 221, about 2.3 times the average. By contrast, in several postcode sectors the incidence of Legionnaires' Disease was more than twenty times the average for the health board (this study). The reports concluded that there was great spatial variation in morbidity and mortality within Greater Glasgow Health Board and much of it was explicable by socio-economic differences. The high morbidity areas for many diseases were similar to those in this report i.e. central parts of Glasgow and east of the city centre.

Clearly, the high incidence of Legionnaires' Disease in Greater Glasgow Health Board, and within parts of Glasgow City, were not solely a result of high susceptibility in the face of equal exposure to legionellae. However, the high incidence probably resulted from relatively high susceptibility together with greater exposure to sources of legionellae.

Spatial clustering is characteristic of point-source outbreaks (Mausner and Kramer, 1985). Cases must have been near the postulated source during the incubation period of the disease. Investigation of the whereabouts of cases may point to the source of infection. Insofar as people tend

to work, socialise and attend hospital near their place of residence spatial clustering by home address could be observed in an outbreak, even when the infection was not acquired at home. For non-outbreak cases we would expect little or no spatial clustering by home address unless some of these cases were infected from a common source, possibly over a prolonged period of time.

Spatial clustering of non-outbreak cases was, however, common (tables 4.15-4.18 and correspondng text) and in some instances there was unequivocal clustering in time too. As such, some of these cases were probably part of outbreaks which had been missed by the surveillance system and cannot be described as sporadic except in the sense that no common link was demonstrated. In other cases, spatial clustering arose from single cases separated by months or years, and these, arguably, were sporadic.

Of these clusters the most notable was that of nine cases which occurred over the period July to September 1983 in Edinburgh postcodes EH6 and EH7. Clearly, an outbreak had been missed; illustrating again that outbreaks are either not noticed or noticed late, by clinicians (Ad-hoc Committee, 1986; Committee of Inquiry, 1986; Bhopal, 1986) and that their detection requires epidemiological surveillance.

The analysis by month of onset and postcode showed that cases of Legionnaires' Disease in G31 did not cease as was

perceived by the investigators (Ad-hoc Committee, 1986): indeed six cases occurred in the period October 1986 to November 1985. It cannot be assumed that these were associated with the G31 outbreak but clearly this finding casts some doubt on one of two conclusions reached by the investigators: that control measures had been effective, or that the source of infection for the outbreak had been traced. The reason why these cases were not recognised as G31 residents and investigated is not wholly clear; in only one of the six was the address on the laboratory form missing or wrong. It appears that cases occurred singly and widely serarated in time, and hence were categorised as "sporadic". Five cases of Legionnaire's Disease lived in the G21 and G22 areas in Glasgow but, as described by MacEwan (1986) and observed by the author, the attitude of the investigators was that these cases were sporadic, and hence did not warrant detailed investigation to seek a common source.

In the two postcode areas G11 and G12 there were 10 cases over several years as follows: 1980 (one case), 1983 (one in February, two in November), 1984 (three cases in August and one in October) and 1985 (one in March, one in April). This provides a striking example of sporadic cases and small clusters in the same area occurring over a prolonged period and hence presumed to be sporadic yet in retrospect were not so. A less striking example is provided by the location and onset of the cases in Tayside Health Board (table 4.15, footnotes (h) and (i).

These observations on space-time clustering have implications for the surveillance of this infection and for the approach to the investigation of apparently sporadic cases which are discussed in section 7 and 8.

What about spatial clustering of travel-associated cases? Most travellers take package holidays and are probably exposed in hotels but other sources cannot be excluded (Bartlett et al, 1986). Travellers, particularly package holiday makers, staying in a particular hotel at one time are likely to come from a limited geographical area. Moreover, a hotel might attract the custom from a few travel agencies and hence cater to clientele from one area, and this relationship could exist over long periods of time. Then, if several cases were infected at a holiday resort, spatial clustering by place of residence could occur even for travel-related cases. Therefore spatial clustering by home address of both outbreak and sporadic cases infected abroad could theoretically occur.

In this study, variation in the incidence of travel-associated disease was observed, but it was less than with non-travel Legionnaires' Disease. The cumulative 9-year incidence rate for travel-related disease was highest in Greater Glasgow Health Board (34 per million) followed by Tayside (26 per million), Highland (22 per million), and Ayr and Arran (21 per million). The overall relative risk to Glasgow residents in comparison to the remaining Scottish

population was 2.2. The excess in Greater Glasgow residents may have resulted from a combination of differential testing, host susceptibility and better surveillance. Alternatively, residents of Greater Glasgow may have travelled to destinations which, at the time of travel, posed a high risk of infection e.g. The Rio Park Hotel in Benidorm, Spain (Grist et al, 1979; Bartlett et al, 1984b). The former explanation may suffice to explain the modest excess risk in Greater Glasgow, but, the latter explanation also needs to be considered. However, in this study, the two cases which apparently clustered in time and space were not acquired in the same country (Ch 4, results e, v).

The comparatively modest variation in the incidence of travel-associated infection provides evidence against the argument that the clustering of non-travel cases resulted from a combination of geographical differences in hospital and diagnostic services, patterns of case-ascertainment or host susceptibility. If so, travel-associated cases would have shown a similar degree of geographical variation as non-travel cases. Of particular interest was the finding that within the Greater Glasgow Health Board the residences of travel-associated cases were scattered and that the post-code sectors with the highest incidence were not in or near the city centre (most people who can afford foreign travel tend not to live in the inner city). By contrast, non-travel cases were clustered in the post-code sectors near the city centre.

The geographical variations between health boards and within the Greater Glasgow Health Board were not satisfactorily explained as either artefact or a result of host differences. Between 1978 and 1986 Greater Glasgow Health Board was the place of residence (or workplace) of all the community-outbreak cases, 36% of the travel-associated cases, and 56% of non-travel, community-acquired, non-outbreak cases. Furthermore, both outbreaks were linked to cooling towers in the north of the city, specifically in the post-code district G31, and most non-outbreak cases lived north of the city, and many in or near G31. What environmental factors could explain these observations?

(4) ENVIRONMENTAL EXPLANATIONS

Ideally, the location of residence and workplace of all cases should be related to the location of all known sources of infection i.e. cooling towers, hot water systems, spas etc. and interpreted with information as to the degree of hazard from each location. However, comprehensive data of this nature do not exist and their collection was beyond the scope of this study.

As part of this study all local authorities in Scotland were asked to provide the addresses of cooling towers within their boundries but these data were not analysed in detail for two reasons. Firstly, many local authorities did not know the location of cooling towers. Secondly, the Glasgow

cooling tower survey showed that unless a premise has been checked by a knowledgeable person the existence of a reported cooling tower could not be assumed. Hence, the role of cooling towers as a source of infection for non-travel cases was properly tested only in the City of Glasgow. Before discussing the results of the Glasgow cooling tower survey, the water supply in the Greater Glasgow area is considered.

One plausible explanation for the variation within Greater Glasgow, that it was a result of variation in the quality of the water supply, was refuted by the observation that the Loch Katrine reservoir supplies water to about 95% of the population. However, could the quality of the water explain the high incidence of Legionnaires' Disease in Greater Glasgow? Though the water source is naturally acidic, the water is rendered alkaline (up to a pH of 9.2) by the addition of lime to counter the problem of plumbo-solvency resulting from the use of lead mains and domestic water pipes. The biocidal action of chlorine is impaired at such a pH (Department of Health, 1989). However, at high pH growth of legionellae is inhibited and ceases above a pH of about 9.2 (Wadowsky et al, 1985; States et al, 1987). However, as the water reaches Glasgow it becomes less alkaline. Chlorine levels in Glasgow are low and were undetectable in the mains water supplied to a Glasgow Hospital (Bryden,1987). Legionellae from source waters are more likely to survive in chlorine-free water and subsequently seed hot water systems and cooling towers.

While these conditions, particularly the low level of chlorination at point of use, might favour the seeding of legionellae into water systems, the Glasgow water supply does not share the other characteristics which foster legionella growth i.e. warmth, river water, organic and inorganic deposits, high iron content and stagnation (Schofield and Locci, 1985a; States et al 1985; Vickers et al, 1987).

The data on the maintenance of domestic water systems at premises with cooling towers, though not based on a representative sample of premises, suggest that such systems were poorly maintained. The possibility that the high incidence of Legionnaires' Disease in Greater Glasgow is related, in some ill-understood way, to the quality of the water supply, and maintenance of domestic water systems, cannot be rejected. However, neither the annual fluctuations in the incidence, nor the geographical variation in Greater Glasgow can be explained by the proposal that domestic water systems were the dominant source of non-travel infection. Now the role of cooling towers is examined.

The Glasgow cooling tower survey was done in 1987 and 1988 but the cases were ill in the period 1978-1986 making interpretation of the association between cooling towers and infection more difficult. Probably, some of the premises with cooling towers during 1978-86 had no towers by the time

of the survey. The effect of this 'error' which could not be corrected (as the presence of cooling towers needs to be confirmed by discussion with engineers or visual inspection) is difficult to assess but would probably be of a false negative nature i.e. would weaken any observed association. To avoid finding spurious associations, only those cooling towers which were known to exist during each year 1978 to 1986, together with the cases in that particular year were analysed for the association between cooling tower location and location of residence. Bacteriological investigation of cooling towers was not done but, though it would have been of interest, it would not have reflected at all the conditions in the period 1978-1986.

The cooling tower survey showed that improvements in maintenance had occurred and, by inference, between 1978 to 1986 maintenance standards were worse. Even by the time of the survey, after much media coverage (Bhopal, 1986), many cooling towers were poorly maintained and potentially a source of legionellae. In particular, drift control was poor. (The maintenance aspects of the survey have been discussed in detail in chapter 7).

The spatial distribution of cooling towers was similar to that of the location of non-travel cases. Most cooling towers were north of the City of Glasgow (and particularly around its centre) and most of those in south Glasgow were close to the River Clyde where most of the industrial areas

of the City are. The main shopping area, which contains many large buildings with cooling towers, lies centrally and is North of the River (see transparency 1 in back folder). Many people work in the main shopping centre but few people live there.

There was a strong association between the location of residence of non-travel cases of Legionnaires' Disease, and the location of cooling towers which was not apparent for travel-related infection (see tables 7.6 and 7.7). The observation that the risk of infection in a population was inversely related to the distance from the nearest cooling tower (a dose-response effect) was striking. Over the period of this study, Glasgow residents living within one-half of a kilometre of any cooling tower had an incidence of disease about three times higher than those living more than one kilometre from the nearest tower. Such risk estimates, derived from a single study, must be guarded. However, it is probable that they underestimate the true excess risk of Legionnaires' Disease associated with proximity to cooling towers for this reason: many of those people who did not live within one kilometre of a cooling tower would, nonetheless, have been exposed to one, either in the course of their work or other activities. To measure the true risk of Legionnaires' Disease the ideal comparison group would be population who were not within one kilometre of a cooling tower during the study period (a group which would, in practice, be impossible to assemble).

The distribution of cases, with the main clusters being east and north of the city centre and the concentration of cooling towers, accords with the fact that the local prevailing wind is south-westerly and hence would promote aerosol movement in a north-east direction (Meteorological Office, 1981). More detailed studies of the wind patterns were not done for the wind is constantly changing and the measurements are taken seven miles away from the city centre. Also, local air currents, which are undoubtedly important could not be accounted for (Oughton, 1987). Presently, this remains an interesting but incompletely investigated observation.

What are the explanations for the relationship between residence of cases and location of cooling towers? Assuming that cooling towers are a source of aerosol causing non-outbreak infection, unbiased underascertainment would cause underestimation of the strength of the association, for populations living close to towers and hence exposed to a higher risk of infection, would be wrongly categorised as unexposed. If, however, cooling towers in areas where cases had occurred were more likely to be ascertained, this bias could explain the association. Between 1978 and 1986, however, Legionnaires' Disease was not notifiable and Environmental Health Officers were not informed about non-outbreak cases. Residence information played little part in the surveillance process. The case and cooling tower location data were collected independently. Though both outbreaks were in the G31 area there was no unduly heavy concentration of cooling towers in this area. The ascertainment bias hypothesis cannot be disproven but needs to be judged against other explanations, including those below.

Cooling towers are associated with large buildings which contain complex hot water systems. Perhaps people living near, shopping, or otherwise visiting or working in such buildings are infected from domestic water systems in these buildings and not from their cooling towers.

However, as aerosol from hot water systems has not been shown to carry over long distance, unlike aerosol from cooling towers, this hypothesis would require that people enter such buildings and pass close to sources of aerosol. Merely living close to such buildings would not be sufficient. As discussed by the Committee of Inquiry (1987), large scale use of domestic hot water systems in shops is unlikely. Also, there is no history of legionella dissemination in this way. Hence, this hypothesis cannot be refuted but seems improbable.

In contrast, the Committee of Inquiry (1987) noted the significant danger of Legionnaires' Disease to customers shopping in centres where there are cooling towers and cited two examples of outbreaks which may have occurred in this way (Nordstrom et al, 1983; Anderson et al, 1986). The few outbreaks which have been linked to office blocks and industrial premises have mostly been associated with cooling towers and not domestic hot water systems (Committee of Inquiry, 1987).

On balance, the evidence is in favour of the hypothesis that cooling towers were an important source of both outbreak and non-outbreak, non-travel infection in the City of Glasgow. This hypothesis offers an explanation for the annual fluctuation (changes in environmental conditions and cooling tower maintenance), the geographical variation within the City of Glasgow (incidence depends on exposure to cooling towers) and the association between the location of

cooling towers and the place of residence of cases (movement of drift into or around homes causes infection). If domestic water systems were the dominant source of non-travel infection none of the above observations can be explained. If this hypothesis were true for elsewhere in Scotland, the geographical clustering of cases and the annual fluctuation in the number of cases could also be explained in terms similar to the above. Next, the evidence is summarised in the context of the epidemiological criteria for causality.

(5) INTERPRETATION OF THE EVIDENCE IN THE CONTEXT OF THE EPIDEMIOLOGICAL CRITERIA FOR CAUSALITY

Interpretation of the evidence about geographical variations in disease incidence and the association between location of residence and location of cooling towers is assisted by application of the epidemiological criteria for causality (Mausner and Kramer, 1985) as follows:

Temporal sequence - the presence of cases in a locality would be unlikely to increase the likelihood of installing a cooling tower there, though the opposite is more likely i.e. the occurrence of cases would inhibit owners of local premises from installing cooling towers.

Strength - a) The association between location of cooling towers within the City of Glasgow and residence of cases of non-travel Legionnaires' Disease was strong. Residents who lived within 500 metres of a cooling tower were about four times more likely

than those who lived more than 1 kilometre away to develop Legionnaire's Disease.

b) There was a dose-response relationship.

Specificity - a) The association between location of cooling towers and residence of cases did not apply to travel-associated cases.

b) the geographical variation in the incidence of Legionnaires disease was far greater than that observed for other respiratory infections including pneumonia.

Consistency - a) the pattern of location of the residence of cases within Greater Glasgow Health Board was similar over different time periods e.g. in the periods 1978-1983 and 1984-1986.

b) The finding of geographical variation was consistent with previous international and regional observations on geographical variation.

Biological plausibility - the survival and viability of legionnellae in aerosol has been recorded in the laboratory and in outbreaks. It is plausible that infection occurred to people who lived, worked or socialised near cooling towers.

Experimental confirmation - controlled experiment is not possible but natural experiment can also provide evidence. Following the outbreaks in Glasgow in 1984 and 1985 only two non-travel cases occurred in 1986. The exceptionally low number may, conceivably, have been related to improved maintenence of cooling towers.

The above analysis, based on the epidemiological criteria for assessing the causality of associations lends credibility to the hypothesis that the association between the location of cooling towers and residence of cases is 'causal' (in the sense that cases of disease arise from transmission of infective material from cooling towers causing infection among people who live near cooling towers).

Now the theoretical and practical implications of the three principal findings are considered: the high incidence of disease in Scotland, the geographical variation and the association with cooling towers.

(6) THEORETICAL ISSUES

As discussed in section 2, the incidence of Legionnaires' Disease in Scotland was high in comparison to England and Wales, the USA and most other countries yet the reported prevalence of antibody in Scottish people has been low (Fallon and Abraham, 1982) and legionellae have infrequently been isolated from cooling towers and other waters (Jackson, 1985; Bhopal, 1986). The evidence did not support the explanation that the higher incidence was solely a reflection of better surveillance or better used diagnostic services.

Legionnaires' Disease appears to be related in a poorly understood way to weather. Scotland's climate is cool and

hence, on first principles, less favourable to the growth of legionellae. In such a climate the need for air conditioning by cooling towers would be relatively low. However, Scotland, and particularly the West of Scotland has a high relative humidity (Meteorological Office, 1981). Might this assist in the survival of organisms in aerosol and hence the infectivity of cooling tower drift? While Scotland may have fewer cooling towers used for air-conditioning than warmer countries, it is traditionally an industrial country where residential and industrial areas are side-by-side. Glasgow is the major city in Scotland and the industrial hub of the country. The density of cooling towers in industrial and hospital premises in residential areas is probably no less than elsewhere (though comparative data were not found), perhaps higher. (Notably, in the Glasgow survey, cooling towers on industrial premises were least well maintained).

In the late 1970's and 1980's the manufacturing industry in Glasgow declined, but there was a great deal of renovation work with demolition, sandblasting and rebuilding. Others have noted the association between construction and earth-work and disease (Thacker et al, 1978; Storch et al, 1979; England et al, 1981). Though its role in Glasgow has not been clarified this offers one possible explanation for the high incidence in the Glasgow area and particularly the east end of the City which has, more than elsewhere, undergone extensive renovation in the last decade.

The paradox of high incidence of disease in the face of low prevalence of antibody and infrequent isolation of legionellae from the environment may be explained by the following (untested) hypothesis: most cooling towers are free of legionellae most of the time but a few are contaminated and cause most of the infection. Possibly, those that are contaminated, harbour virulent forms of organism. Alternatively, it may be that the low isolation rate from the environment reflects insufficiently stringent methods of detection.

The susceptibility of the Scottish population to Legionnaires' Disease may be somewhat higher for both known reasons e.g. the high prevalence of smoking (Balarajan and Yuen, 1986) and more socio-economic deprivation, and unknown reasons. Notably, for any level of consumption of cigarettes the incidence of lung cancer is higher in the West of Scotland population than in other places (Gillies, et al, 1988). However, higher susceptibility offers no more than a partial explanation for either the high incidence of Legionnaires' Disease in Scotland or the geographical variation.

The variation in the incidence between health boards and towns offers a means of developing and testing hypotheses on the source and mode of transmission of infection of non-outbreak Legionnaires' Disease cases, and,

on first principles, offers hope that even non-outbreak disease is preventable (Rose, 1987).

Past experience of outbreaks (Ad hoc Committee, 1986; Timbury et al, 1986) and the present studies in Greater Glasgow Health Board provide evidence that in this area cooling towers were a principle source of infection for all types of non-travel infection. The pattern of distribution of cases was not compatible with the hypothesis that non-outbreak, non-travel infection was predominantly acquired from domestic water systems. Previous evidence concerning the source of infection for non-outbreak (or sporadic) cases implicates domestic water systems (Stout et al 1987; Joly and Winn, 1984) and this is the first report of non-outbreak infection linked to cooling towers.

The data do not permit conclusions on the place at which infective aerosol is inhaled. Insofar as people tend to work, shop or socialise near their homes the association between place of residence and location of cooling towers may reflect either, or both, infection inside and outside the home. Studies based on better data on the whereabouts of cases prior to illness are required to establish accurate, quantitative estimates of the association between location of cooling towers, and place of residence and workplace. As many patients were unemployed or retired and some were housebound prior to their illness, infection does occur in, or near home, rather than at work (see also, Ad-hoc Committee, 1986). Also, the pattern of distribution of

non-travel, non-outbreak disease was the same for men and women and for people of working age and those likely to be retired (figures 4.11 and 4.12). The implication is that aerosol is carried a considerable distance from the cooling tower and retains its infectivity. The plausibility of this is now reviewed.

Particles of more than 100 microns settle rapidly but smaller ones, in favourable conditions, may be suspended in air and travel by diffusion, sedimention and with air currents. Journeys of hundreds of kilometres have been recorded in conditions of laminar flow of air currents (Bovallius et al, 1980). Turbulence reduces distant travel and, within an urban environment this is inevitable. Our hypothesis requires that aerosol travels a modest distance, say a maximum of one kilometre, yet that concentration of microorganisms remains sufficient to cause infection.

The warm drift from a cooling tower will rise but its eventual descent will occur as a result of convection currents, the cooling effect of evaporation which lowers the drift temperature and temperature inversion layers (Cox, 1987; and Mr. James Alladyce (principal meteorological officer, personal communication)). Low level inversions are an autumn, winter and spring phenomena but summer inversions can also occur. Under conditions of low turbulence (winds of less than two miles per hour) an aerosol pocket can rise from the ground, move horizontally

and descend but remain relatively intact (Cox 1987; Mr. J. Alladyce, personal communication).

Laboratory data on the hardiness of legionellae in aerosol indicate that organisms might remain viable during such a journey (Hambleton et al, 1983) but dessication would be the principle hazard (Bovallius et al, 1980; Cox, 1987). We may speculate that legionellae may be further protected by the chemicals produced by algae (Berendt, 1981) or by carriage within amoebae or other organisms (Rowbotham, 1980, 1984, 1986). It is notable that water particles in aerosol evaporate completely in less than a second but droplet nuclei with micro-organisms do not, though they may be reduced to a tenth of their original size (Morrow, 1980; Riley, 1980). Hence particles of about 10-30 microns (about the size of an amoeba) ejected from cooling towers may be large enough to allow the survival of legionellae, and yet, through dessication, become small enough to be inhaled into the lungs. However, once inhaled, the particles will be rehydrated and may become too large to be inhaled into the alveoli (Cox, 1987).

If Legionnaires' Disease is transmitted over distances of hundreds of metres then, by inference, the infective dose must be relatively small. But, the lack of person-to-person spread suggests (but does not prove) a large infective dose and so do animal experiments. Guinea-pigs need to inhale thousands (2,400-490,000) of organisms to acquire lethal pneumonia while a million organisms are

needed to induce fever and microscopic pulmonary lesions in monkeys (Baskerville et al, 1981). Aerosol sources produce low concentrations of organisms of the order of 100,000 organisms per cubic metre (Bovallius et al, 1981; Tyndall et al, 1982a; Tyndall et al, 1985). However, the infective dose for humans may be much smaller than for laboratory animals for three reasons: higher susceptibility of man as compared to laboratory animals, the high susceptibility of people with risk factors, and the possibility that the infective dose is lower when legionellae are inhaled as a packet within larger organisms such as amoebae. Nonetheless, our understanding on the infective dose indicates that infection is more likely during the longer term exposure which occurs at home or at work rather than the casual exposure experienced by the passer-by. This inference does not preclude infection after casual exposure which is well documented (see below).

The above concepts have not been verified in the context of Legionnaires' Disease, particularly for non-outbreak infection, but seem credible. Observations of long-distance transmission of other infections and epidemiological observations during outbreaks of Legionnaires' disease (see table 2.6) add to the plausibility of the hypothesis.

While legionellae have never been cultured from cooling tower drift at a distance, the epidemiological evidence

shows that contaminated drift travels modest distances to cause infection (see Table 2.6 and corresponding text). In the outbreak described by Klaucke and colleagues (1984) the drift travelled about 150 metres. In the Glasgow community outbreak, two patients who were housebound lived 700 and 900 metres from the presumed source of infection and were, presumably, infected in their homes (Ad-hoc Committee, 1986). More recently, the outbreaks associated with the BBC headquarters in London (PHLS, 1988), Leicester Square in London (PHLS, 1989), a hospital in Barcelona (Monforte et al, 1989), and Woolongong, Australia (Christopher et al, 1987) included cases who were infected while visiting the area but not entering buildings. In the London outbreaks there were patients who were probably infected at home (PHLS, 1988; Dr C L R Bartlett, Lecture to the British Society for the Study of Infection, 1989).

Drift presumably enters homes through open windows, doors, air vents, chimneys or other fresh air intakes. In the outbreak at St Elizabeth's Hospital, Washington, there was an association between having a bed near a window and disease (Thacker et al, 1978). In the Dennistoun outbreak in Glasgow the postal case-control study, but not the neighbourhood case-control study, showed an association between sleeping near an open window and developing Legionnaires Disease (Ad-hoc Committee, 1986).

The hypothesis advanced, that cooling tower drift was the source of infection for much of the non-outbreak

infection in the City of Glasgow area, and that proximity to a cooling tower was the explanation for the variation in disease incidence, is compatible with existing evidence on the physics of aerosol movement, the ecology of the organism and the epidemiology of the infection.

Now the practical implications of this study for the future surveillance and prevention of Legionnaires' Disease are considered.

(7) RECOMMENDATIONS ARISING FROM THIS RESEARCH FOR THE SURVEILLANCE AND PREVENTION OF LEGIONNAIRES' DISEASE

The importance of effective surveillance is emphasised by this study. The Scottish system "missed" several clusters of cases of which the most important were those in Edinburgh in 1982 and 1983, in the G21 postcode sector in Glasgow and the G31 cases following the 1984 outbreak, and most of the possible non-outbreak, nosocomial cases. Clearly it needs to be strengthened. Clinical observation alone cannot pick up clustering, partly because laboratory forms do not always have date of onset and address. Computerisation of test results has been implemented at the acting reference laboratory. The next step should be to develop a system of routinely collecting data on date of onset, postcode of residence and workplace for all cases and do analysis to seek space and time clustering. Such analysis should be on a regular basis. Mapping should, in the first instances, be of the point-pattern type in order to seek obvious patterns. Chloropleth mapping is constrained by arbitrary boundaries and there is a danger of falsely concluding that no clustering exists e.g. when cases are close together but in adjacent postcode sectors.

The value of centralised testing has been confirmed, not only for on-going surveillance but also for retrospective research. This study would have been cumbersome and costly (perhaps impossible in practice) if the starting point had been a retrospective examination of

laboratory forms in all Scottish microbiology laboratories instead of at one. The importance of the proper completion of the laboratory request form by the requesting doctor needs further emphasis (see appendix 3). The wider availability of adhesive pre-printed labels would improve identification data but a systematic means of collecting complete information on onset of illness, travel history, workplace, and the whereabouts of the patient prior to illness needs to be devised. Only with this information can a decision be made as to whether a single case requires further investigation. The disease is potentially preventable and each case should be investigated at least until it is clear that it is not part of a cluster. Further , as sporadic cases may herald clusters to come, such a policy could prevent outbreaks (Helms et al, 1984a; Timbury et al, 1986). The need for the above data and approach is a cogent argument in support of making Legionnaires' Disease pneumonia notifiable. In Scotland, the disease was made notifiable in October 1988. (A new review of notification and surveillance of infection is currently underway in England and Wales).

When Legionnaires' Disease occurs the first priority for environmental investigation in Glasgow, and perhaps Scotland, should be the cooling towers in the vicinity of the home, workplace or other suspected place of infection rather than domestic water systems or other potential sources. In the past much energy and resources have been

deflected on collecting water specimens from unlikely sources (Jackson 1985, Bhopal 1986).

Most important of all this study indicates that much of non-travel, non-outbreak Legionnaires' Disease is preventable by improvement in the maintenance of cooling towers, and particularly the control of cooling tower drift. The low level of chlorine, especially in the context of relatively high pH levels, in the Glasgow water supply at the point of use should be recognised and solutions sought. Finally, pending further surveys, it should be assumed that domestic water systems in most large premises are not maintained in accord with the standards expected in health care premises (Department of Health and Social Security, 1987 and 1988). However, in terms of prevention, improvement in maintenance of domestic water systems in non-health premises is a relatively low priority at present.

Monitoring of the maintenance of cooling towers is needed but cannot be done until the location of cooling towers is known. It cannot be assumed that media publicity, alone, will suffice in achieving proper maintenance. Hence field work based surveys of cooling towers will be necessary (supported by postal surveys (Baxter, 1985)), perhaps using maintenance scores similar to those described earlier to identify towers which are poorly maintained. At many premises those responsible for cooling tower maintenance need impartial advice and literature on maintenance procedures.

8. RECOMMENDATIONS FOR FUTURE RESEARCH

A great deal of research on the epidemiology of Legionnaires' Disease has been done but many gaps in knowledge have been highlighted in the literature review. Discussion now will be confined to those areas of research which are directly relevent to this work.

Epidemiology depends on a surveillance system which provides valid and complete data which, preferably, are collected prospectively. As already stated, information on the location of residence, place and type of work and whereabouts of cases during the incubation period should be routinely collected. In a research context, investigation of the home, work and social environment of non-outbreak cases should also take place together with appropriate bacteriological investigation. Hypotheses regarding the mode of infection and especially the importance of workplace could then be tested. The comparison of cases with controls would be the next logical step, particularly to measure the degree of risk. The case-control study design is well suited for both testing hypotheses and measuring risk. Control groups should be matched for age, sex and past health experience. Hospital patients with other respiratory diseases, including confirmed pneumococcal pneumonia, acute bronchitis and lung cancer could be the control group. (A control group with a mix of diagnosis would be preferable to a single diagnosis and, in view of the rarity of Legionnaires' Disease each case should be matched with three or four controls, (Kahn, 1983).

This study has considered only *L pneumophila* infection. Possible infections by non-*L pneumophila* species were excluded because of the doubts about the validity of the diagnosis by serology. It would be of interest to see whether spatial clustering was a characteristic of such cases. If so, this would be epidemiological evidence that these patients have pneumonias caused by *Legionella* species and that the serological changes are not a non-specific reaction to other infection.

The validity and importance of the findings of this study can only be judged after the research strategy has been applied in other places. The established and thorough surveillance scheme in England and Wales offers the opportunity for such study. The incidence of disease could be studied in each of the health regions and districts and at a small area level in places where there is a high incidence. Again, the cases should be categorised by travel history, outbreak history and exposure to a hospital and incidence rates calculated in each group. Information on the organisation of diagnostic services and their use by clinicians (including the numbers of serology tests requested) would be required to test the differential testing hypothesis (as in chapter 5). Data on the number of patients admitted to hospitals with pneumonia could be extracted from the hospital in patient information systems which are similar to those in Scotland. In principle, this study could be repeated in England and Wales. To date, the

weight of evidence suggests that most outbreaks in England and Wales, in contrast to Scotland, have been related to domestic water systems and, as such, it seems apt to study whether this also applies to the larger number of sporadic cases.

A population based survey of prevalence of antibody by place of residence could, theoretically, dispel or confirm the view that the geographical variation in disease is an artefact. One would predict that the geographical variation would correspond to that of the incidence. If not, then this would be strong evidence for artefact as the underlying explanation of the variation in incidence. However, in view of the low prevalence of antibody in the population a truly representative survey would need to be very large, hence expensive and unlikely to be done. However, by judicious sampling of sera already collected (for example blood donations or sera from patients shown not to have legionellosis) a geographical study of this kind could be done.

The relationship between location of residence of non-outbreak cases and location of cooling towers needs to be verified in other cities, both in Scotland and elsewhere. Accurate and verified data on location of cooling towers will need to be collected and as, within the United Kingdom, London is the city where such data are most likely to be collected further studies may be possible there.

The cooling tower maintenance study should be repeated in Glasgow, after a suitable delay, to assess whether further improvements in cooling tower maintenance have occurred, and if so, whether the incidence of locally-acquired disease has further diminished. Microbiological surveys of cooling tower water would be of value but only if testing was repeated, and not only done on one occasion (Grow et al, 1984). Then, light might be shed on the relationship between the maintenance and design of a cooling tower system and its bacterial ecology.

As a measure of risk, the concept of maintenance scores merits further study. The relevant question is this: which of the components of the score best predict a risk of Legionnaires' Disease, and as an interim measure of risk, which components relate to colonisation of the system by legionellae? The aim would be to reduce the amount of information to be collected in surveys which monitor cooling towers yet improve the ability to pick out cooling towers which pose a hazard.

Tracer smoke studies have been useful in showing the movement of aerosol from cooling towers to air intakes in the investigation of outbreaks. However, though they might produce interesting results, particularly in regard to local air currents in an urban environment, such studies would be unlikely to yield insight into the spread of infection from cooling towers in the case of non-outbreak infection.

A number of other areas where research is needed have been noted earlier: the unusual seasonal variation in Scottish cases, the possible importance of climate in the growth, dissemination and risk of Legionnaires' Disease, and the possibility that the virulence of organisms differs geographically. These are complex and difficult research areas. Nonetheless, they need to be studied, not by the practitioner of a single discipline but in collaboration.

The analysis of clustering, and particularly the techniques for both quantifying the association between geographical location of cases and location of the putative source and demonstrating causality, is at an early stage of evolution (Elliott, 1989). This is the domain of the spatial statistician but the medical epidemiologist is well placed to seek out important problems for the statistician and to make suggestions to their solution in general terms. Presently, more detailed analysis of the data presented in this thesis is underway in collaboration with statisticians. An early step will be to repeat the analysis shown in tables 7.6 and 7.7 with other respiratory disorders to assess whether the relationship is specific.

Legionnaires' Disease is a complex infection and the scope for research is wide. For the advancement of the approach and the principle hypothesis of this work the following are proposed a priorities:

(a) The repetition of this work in another place;

(b) The development, implementation and evaluation of a computerised information system suitable for use by laboratory staff and those involved in surveillance, which allows easy analysis of spatial and temporal data. The system would be used not only for Legionnaires' Disease but also other diseases;

(c) A case-control study examining the home environment, nature of work, social circumstances and whereabouts of cases of Legionnaires' Disease prior to their illness;

(d) Further work on the location and quality of maintenance of cooling towers, the bacterial ecology of such systems, and the incidence of disease, particularly in locations outside Glasgow.

The underlying aim of this research was to advance knowledge on the source of non-outbreak, locally-acquired Legionnaires' Disease, and hence help in its prevention. To what extent this aim has been achieved is a judgement for the future. However, an approach for the epidemiological study of the problem, based on the observation and explanation of geographical variation in disease incidence, has been developed, tested and found to be fruitful. Should colleagues find the approach and findings of this thesis of value to their work, and are stimulated to seek improvements in the method and to apply the results, this research journey will not have been in vain.

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Notes

a) The literature search was concluded in June 1989.

b) Where "Legionella pneumophila" and "Legionella" were not italicised in the original paper (eg Lancet papers) they have not been italicised here.

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APPENDICES

APPENDIX 1

THE PROPORTION OF SMOKING WHICH MAY BE PREVENTABLE BY STOPPING SMOKING: AN ESTIMATE BASED ON ATTRIBUTABLE RISK

Population attributable risk is a concept by which the proportion of disease incidence attributable to a causal risk factor can be estimated. The attributable risk indicates the decrease in disease incidence which could arise if such a risk factor were no longer present. While the association between smoking and Legionnaires' Disease has not been unequivocally demonstrated to be a causal one, nonetheless it is likely to be so, though the strength of the association is debatable.
In chapter 2, part 3(a) it was stated that about one-third of the Legionnaires' Disease incidence is preventable through a decrease in smoking. The formula for calculating attributable risk is as follows

$$\text{Attributable risk} = \frac{b\,(r-1)}{b\,(r-1) + 1}$$

where b represents the proportion of the population with the risk factor and r is the relative risk.

(from, Lilienfeld and Lilienfeld, 1980).

Assume that 40% of the population at risk smoke cigarettes and that the relative risk of Legionnaires' Disease amongst smokers is two. Then, 29% of the incidence of the disease is attributable to smoking.

APPENDIX 2

STATISTICAL METHODS USED BY LINEMAP

The method used by LINEMAP for age and sex adjustment of rates is that of direct standardisation whereby the observed rate, in each 5-year age group and each sex, for each geographical region concerned, is applied to a standard population. For health boards the standard population was that of Scotland (1981 census). The result of the calculation is the rate which would have been observed in the health board concerned if its population structure had been the same as the Scottish population. The standardised rates for postcode sectors are calculated in the same way. However, the standard population used in such analysis was an appropriate local population e.g. for GGHB and Glasgow City postcode sector analysis the GGHB poulation was the standard. The formula used is:

$$(\text{Standard Rate})_k = \frac{\sum_{i,j} S_{ij} \times \frac{N_{ijk}}{P_{ijk}}}{\sum_{i,j} S_{ij}}$$

Where, N_{ijk} = Number of people in age group i, of sex j living in sub-area k with a particular illness within a given time period.

P_{ijk} = Population of sub-area k, of sex j and age group i.

S_{ij} = Standard population of sex j and age group i.

R_{ij} = Standard incident rate for a particular illness for sex j and age group i (per capita) over a given time period.

The standardised morbidity ratio for Legionnaires' Disease is simply the ratio of observed to expected cases. The expected cases are calculated by applying the rates in the larger region, say Scotland, to the sub-region of interest e.g. GGHB.

The formula used is:

$$(\text{Standard Ratio})_k = \frac{(\text{Actual Cases})_k}{(\text{Expected Cases})_k}$$

where $(\text{Actual Cases})_k = \sum_{i,j} N_{ijk}$

$(\text{Expected Cases})_k = \sum_{i,j} R_{ij} P_{ijk}$

The significance levels derived by LINEMAP are derived from the Poisson distribution. To quote Mr F Nimmo's notes

"The significance levels are derived from a Poisson distribution with a parameter equal to (expected cases)k. The probabilities are summed from the bottom up, starting at value 0, up to and including the value=(actual cases)k. A slight adjustment is then made for technical reasons- half of the probability at value = (actual

cases)k is subtracted from the sum. The result is the first significance level output by the program.

The second significance level depends on the number of sub-areas being standardised (say M). The formula for calculating the second significance level is:

Second significance level=

MIN [0.5, 1 - (1 - Signif Level)^{M}] if Signif Level <0.5

MAX [0.5, (Signif Level)^{M}] if Signif Level >0.5"

This method of adjusting for multiple comparisons is best illustrated by an example. Assume that the level of statistical significance is set at 0.05. Now if in one post code sector in an imaginary area which has 8 postcode sectors, the incidence rate was high and the significance level was 0.9995 the adjusted appropriate significance level would be $(0.9995)^{8}$ which is 0.996. This method is stringent. In this report both unadjusted and adjusted significance levels are given. Probability levels of >0.5, as derived by the computer program, have been presented as 1-p.

APPENDIX 3

INFORMATION NOT OBTAINED FROM LABORATORY FORMS

Microbiology laboratories have an important role in the surveillance of infection and in particular for the early detection of outbreaks. To fulfil this task, laboratories need accurate and adequate identifying and clinical information which must be provided by doctors requesting investigations. Spatial and temporal clustering, based on an appropriate address and date of onset respectively, are the principal indicators of an outbreak. Unfortunately, these data are often absent in laboratory request forms. For the first 400 of the patients studied the missing data on the laboratory request form were noted.

Table A1 shows that for 47% of cases the address was not included on the form. Absence of address was associated with absence of other identification data (e.g. hospital number) and clinical information. Over the 10 year period 1977 to 1986 there was little suggestion that forms were more carefully completed.

There was variation from one hospital to another but two generalisations could be made: a) the use of pre-printed gummed labels raised substantially the quality of identification information, b) where samples were

referred by another laboratory with a new request form or letter both identification data and clinical data were minimal (a laboratory reference number was usually present). For example, in 39 such requests from 3 laboratories the address was absent in 36.

The improvement in information in the period 1984-1986 was mainly due to the increasing proportion of forms coming directly from Glasgow hospitals.

The lessons are clear. Clinical staff should be aware that the address (and date of onset) of the patient may provide early evidence of an outbreak and should ensure that this information is provided to the laboratory (the plentiful supply of pre-printed gummed labels may hold a partial answer). Laboratory staff, who cajole clinicians to provide more information should also ensure that all relevant information is forwarded with specimens to the reference laboratory. Better still, a copy of the original request form should be sent.

The incompleteness of information provided on request forms hinders the surveillance function and may prevent the detection of outbreaks.

TABLE A.1

PROPORTION (%) OF PATIENTS ON WHOM SPECIFIED INFORMATION WAS NOT OBTAINED FROM LABORATORY REQUEST FORMS

Information	Time period			
	1978-1980 (N=80)	1981-1983 (N=94)	1984-1986 (N=226)	ALL (N=400)
Date of birth/age	70	59	40	50
Sex	1	0	0	1
Address	63	60	36	47
Hospital number	21	41	28	30
Consultants' name	48	60	56	55
General practitioners' name	100	100	96	98

APPENDIX 4

RELATIONSHIP OF HEALTH BOARD OF RESIDENCE AND HEALTH BOARD OF HOSPITALISATION

For 443 cases of possible Legionnaires' Disease the health board of residence and of hospitalisation were compared. Eighty nine percent of the cases were hospitalised in the health board in which they lived, as shown in table A.2. For some health boards the proportion was lower, but rose a little when nosocomial cases were excluded e.g. in Ayr and Arran Health Board it rose from 50% to 64% and in Argyll and Clyde from 65% to 69%.

On the basis of these results, it was felt justifiable to guess, from the place of hospitalisation, the probable health board of residence of the six cases of Legionnaires' Disease whose address was not available but who lived in Scotland.

Further details of this procedure and its wider implications for surveillance of infection have been published (Bhopal,1989).

TABLE A.2. RELATIONSHIP BETWEEN HEALTH BOARD OF RESIDENCE AND HEALTH BOARD OF HOSPITAL.

	HEALTH BOARD OF HOSPITAL OF ADMISSION														PROPORTION OF CASES TREATED WITHIN THEIR HEALTH BOARD OF RESIDENCE
HEALTH BOARD OF RESIDENCE	G G	L	LA	A&C	T	F	A&A	F.V.	H	G	B	D&G	NOT HOSPITALISED	ROW TOTAL	
GREATER GLASGOW	244		1	1									2	248	98
LOTHIAN		51											2	53	96
LANARKSHIRE	13		27		1									41	66
ARGYLL AND CLYDE	4		1	11									1	17	65
TAYSIDE	1				11	3								15	73
FIFE		1				8								9	89
AYR AND ARRAN	8			1			9							18	50
FORTH VALLEY	2						1	10						13	77
HIGHLAND									9					9	100
GRAMPIAN										4				4	100
BORDERS		1									6			7	86
DUMFRIES AND GALLOWAY		1										4		5	80
WESTERN ISLES									1					1	0
ORKNEY		1												1	0
NOT SCOTLAND	1										1			2	0
PROPORTION WHO WERE LOCAL RESIDENTS	89	93	93	85	92	73	90	100	90	100	86	100			
COLUMN TOTAL	273	55	29	13	12	11	10	10	10	4	7	4	5	443	89

APPENDIX 5

REASONS FOR EXCLUSION FROM THIS STUDY OF SOME PATIENTS ON RUCHILL HOSPITAL LABORATORY AND COMMUNICABLE DISEASE SCOTLAND UNIT CASE LISTS

Fifty four patients were classified as possible cases. The reasons for not including 37 of them as cases were as follows:

eight had clinical or laboratory evidence of another form of pneumonia or respiratory illness;

12 had serological evidence of non-*L pneumophila* infection (eight to serogroup p185, two to *L.Longbeachae*, and one to each of *L. Micdadei* and *L. Tatlock*);

17 had a static titre of 64 or 128.

The other 17 met the laboratory criteria of infection as shown in table A3. For three of these patients the clinical history could not be obtained despite written and telephone attempts to contact consultants and general practitioners. The others had either an illness without lower respiratory tract infection or were asymptomatic.

A further 24 patients were classified as "unlikely of unclear" cases at an early stage of the study. Of these, 17 had a static serological titre of less than or equal to 128. Of the other six, three patients had no illness and three had non-respiratory illness which consultants stated was not Legionnaires' Disease.

TABLE A3

EVIDENCE FOR INFECTION FOR 17 PATIENTS WHO MET SEROLOGICAL CRITERIA FOR LEGIONAIRRES' DISEASE BUT WERE NOT CATEGORISED AS CASES.

Serological titre	D.F.A. result	Pneumonia
Four-fold titre group		
64	-ve	No
128	"	"
128	"	"
Four-fold drop in titre group		
128	-ve	No
256	"	Unknown
256	"	No
Static titre group		
256	-ve	Unknown
"	+ve	No
"	-ve	"
"	"	"
"	"	"
"	"	"
"	"	Unknown
512	"	No
512	"	"
512	"	"
512	"	"

APPENDIX 6

DETAILS OF HOSPITAL EXPOSURE FOR 16 POSSIBLE NOSOCOMIAL CASES

Sixteen nosocomial cases of Legionnaires' Disease were recorded as part of the Glasgow Royal Infirmary outbreak (Timbury et al, 1986) of which 13 were categorised as cases in this study and three as possible cases. For 16 other patients there was some evidence of exposure to a hospital. (A few of these cases were recognised to be nosocomial prior to this study.) Some details of these cases are in table A.4.

For some patients the evidence of nosocomial infection was slim, but nonetheless, cast doubt as to whether these were community-acquired cases. It is noteworthy that the Glasgow Royal Infirmary had been associated with nosocomial infection prior to the 1985 outbreak.

TABLE A4

DETAILS OF NON-OUTBREAK, CASES WITH HOSPITAL EXPOSURE

Year of illness	Hospital	Evidence	Previously recognised
1983	Glasgow Royal Infirmary	Pneumonia 11 days after admission	No
1983	Glasgow Royal Infirmary	Had stitches removed 10 days prior to illness	No
1983	Gartloch, Glasgow	Long stay inpatient	No
1985	Southern General Hospital, Glasgow	Pneumonia followed elective admission	No
1986	Law Hospital, Lanarkshire	Post-operative chest infection	No
1984	Aberdeen	Secondary pneumonia in immunocompromised patient	No
1984	Stobhill Hospital, Glasgow	Nurse on duty	No
1984	Glasgow Royal Infirmary	Pneumonia following inpatient stay in lymphoma patient	No
1984	Glasgow Royal Infirmary	Consultant anaesthetist	Yes
1985	Edinburgh Royal Infirmary	Pneumonia followed hospitalisation	No
1985	Western Infirmary, Glasgow	Post-operative pneumonia	Yes

1985	Victoria Infirmary, and Glasgow Royal Infirmary	Admitted with renal failure and developed Legionnaires' Disease	No
1985	Royal Alexandra Infirmary, Paisley	Post-operative pneumonia	No
1985	Glasgow Royal Infirmary	Employee at hospital. On steroids	No
1985	Victoria Infirmary, Glasgow	Post-operative pneumonia	No
1985	Glasgow Royal Infirmary	Visited wife at GRI. Wife died from pneumonia (aetiology unknown).	No

APPENDIX 7

THE SCOTTISH HEALTH BOARDS: BACKGROUND INFORMATION

Since 1974 the health service in Scotland has been administered on the basis of 15 geographically determined units, called health boards. The boards vary greatly in their size, population and other characteristics such as urbanisation. Four of the boards have medical schools, namely, Greater Glasgow, Lothian, Tayside and Grampian.

Excepting Strathclyde Region, other local government regions have the same geographical boundaries as the health boards. Within Strathclyde Region's boundary lie Greater Glasgow, Lanarkshire, Ayrshire and Arran and Argyll and Clyde Health Boards. Some census statistics are published for local government regions (or districts) and hence are not available separately for the four health boards in Strathclyde Region.

Figure A1 is a map which shows the location of the Scottish Health Boards. The population (1981 census) of Scotland and the health boards and population density (persons per hectare) is given in table A5. The population density varies enormously and, in particular, the Strathclyde Region figure disguises major variations. The most densely populated local authority district in Scotland was Glasgow City with 38.77 persons per hectare, compared to the next highest, 16.76 persons per hectare in Edinburgh City.

FIGURE A1 MAP OF SCOTLAND AND THE BOUNDARIES OF THE SCOTTISH HEALTH BOARDS

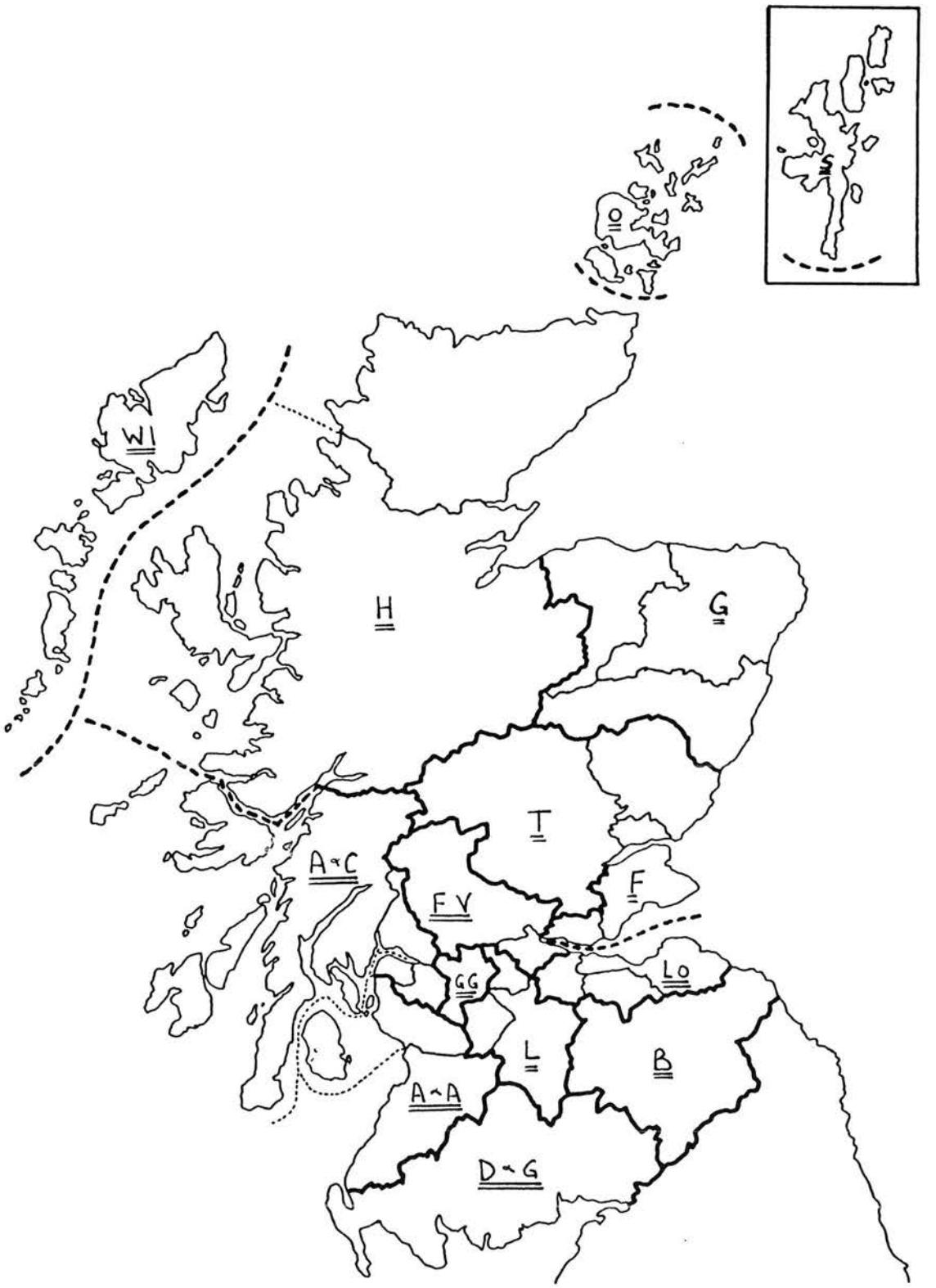

TABLE A5

POPULATION AND POPULATION DENSITY OF SCOTTISH HEALTH BOARDS

Area	Population	Population density*
Scotland	5,149,500	0.66
Argyll and Clyde	452,421	1.78**
Ayrshire and Arran	374,112	1.78**
Borders	100,470	0.21
Dumfries and Galloway	144,218	0.23
Fife	340,182	2.5
Forth Valley	273,012	1.04
Greater Glasgow	1,001,826	1.78**
Grampian	483,000	0.54
Highland	191,966	0.08
Lanarkshire	570,108	1.78**
Lothian	746,056	4.21
Orkney	18,862	0.20
Shetland	25,892	0.19
Tayside	396,825	0.52
Western Isles	30,550	0.11

* Persons per hectare.

** Strathclyde Region figure.

APPENDIX 8

CHARACTERISTICS OF THE GLASGOW WATER SUPPLY.

Table A.6, supplied by the Strathclyde Region Water Department, summarises the physical and chemical characteristics of the water supply to the City of Glasgow and much of the surroundings.

TABLE A6

CHARACTERISTICS OF THE GLASGOW WATER SUPPLY* EX-WORKS

STRATHCLYDE REGIONAL COUNCIL WATER DEPARTMENT

TYPICAL CHEMICAL ANALYSIS - LOCH KATRINE

Colour (Hazen)	10
Turbidity (F.T.U.)	0.47
pH	7.7
Conductivity (uS/cm)	42
Chloride (mg/l)	6
Sulphate (mg/l)	4
Silica (mg SiO2/l)	0.9
Phosphate-soluble reactive (ug P/l)	<5
Fluoride (ug/l)	<50
Calcium (mg/l)	3.8
Magnesium (mg/l)	0.8
Sodium (mg/l)	3.5
Potassium (mg/l)	0.3
Aluminium (mg/l)	<0.02
Total Hardness (mg CaCO3/l)	13
Alkalinity (mg CaCO3/l)	7
Nitrate (mg NO3/l)	0.80
Nitrite (mg NO2/l)	<0.01
Ammonia (mg NH4/l)	<0.02
Total Organic Carbon (mg/l)	1.9
Iron (ug/l)	53
Manganese (ug/l)	<5
Copper (ug/l)	<5
Lead (ug/l)	<10
Free Chlorine (mg/l)	0.2
Total Chlorine (mg/l)	0.2

MEAN VALUES - - - 1987

OTHER ELEMENTS - TYPICAL VALUES

Zinc (ug/l)	<10
Arsenic (ug/l)	<1
Cadmium (ug/l)	<1
Chromium (ug/l)	<1
Mercury (ug/l)	<1
Nickel (ug/l)	<1
Selenium (ug/l)	<2

ALL VALUES EX-WORKS

* Courtesy of Strathclyde Regional Council Water Department

MAP OVERLAYS

For several reasons the map overlays are approximately, rather than exactly, the size of the maps. The GGHB maps in the text vary in size. However, the transparency is an approximate fit to the point-pattern part of figure 4.4.

BHOPAL, R.S.
M.D. 1991

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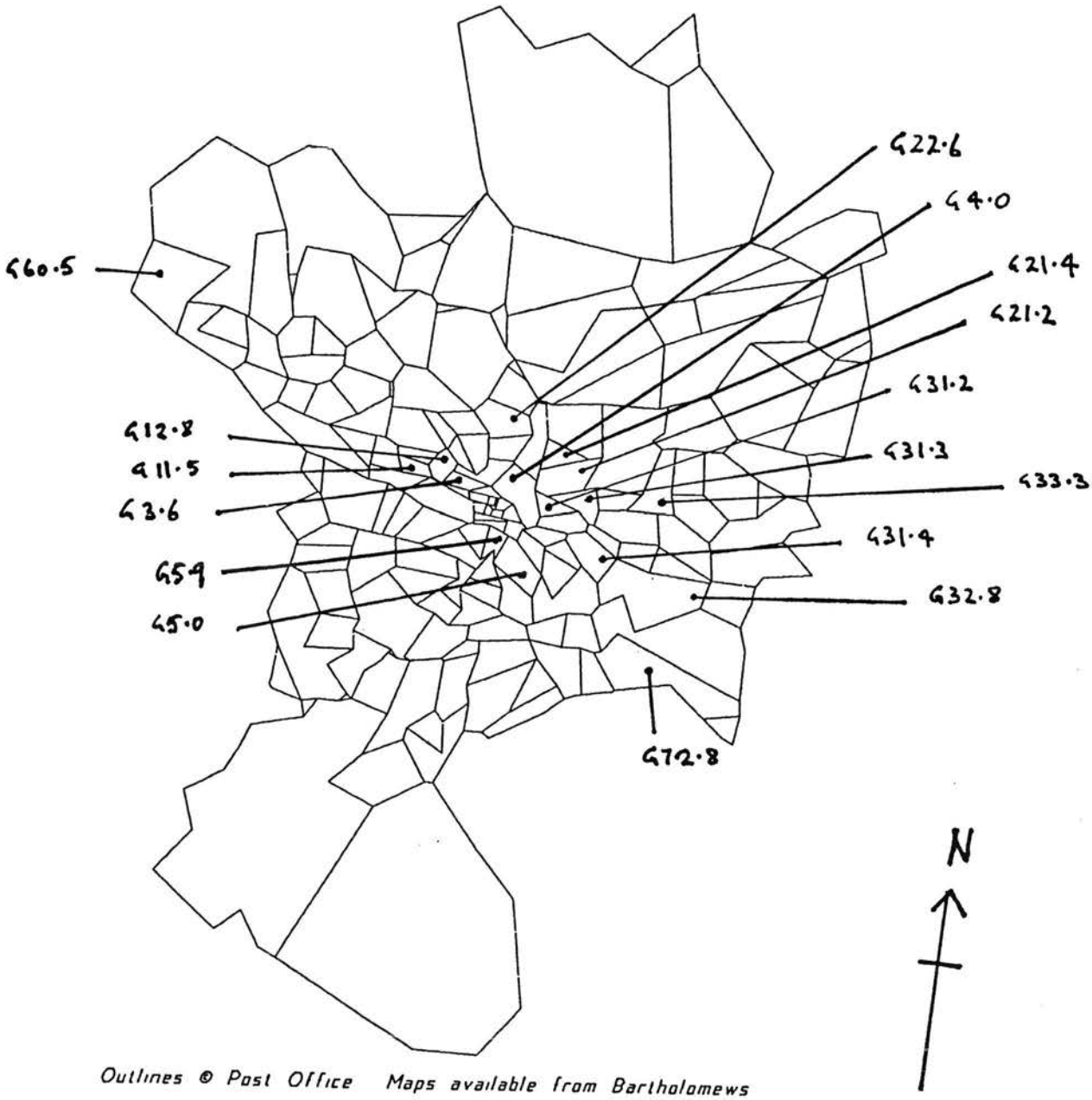
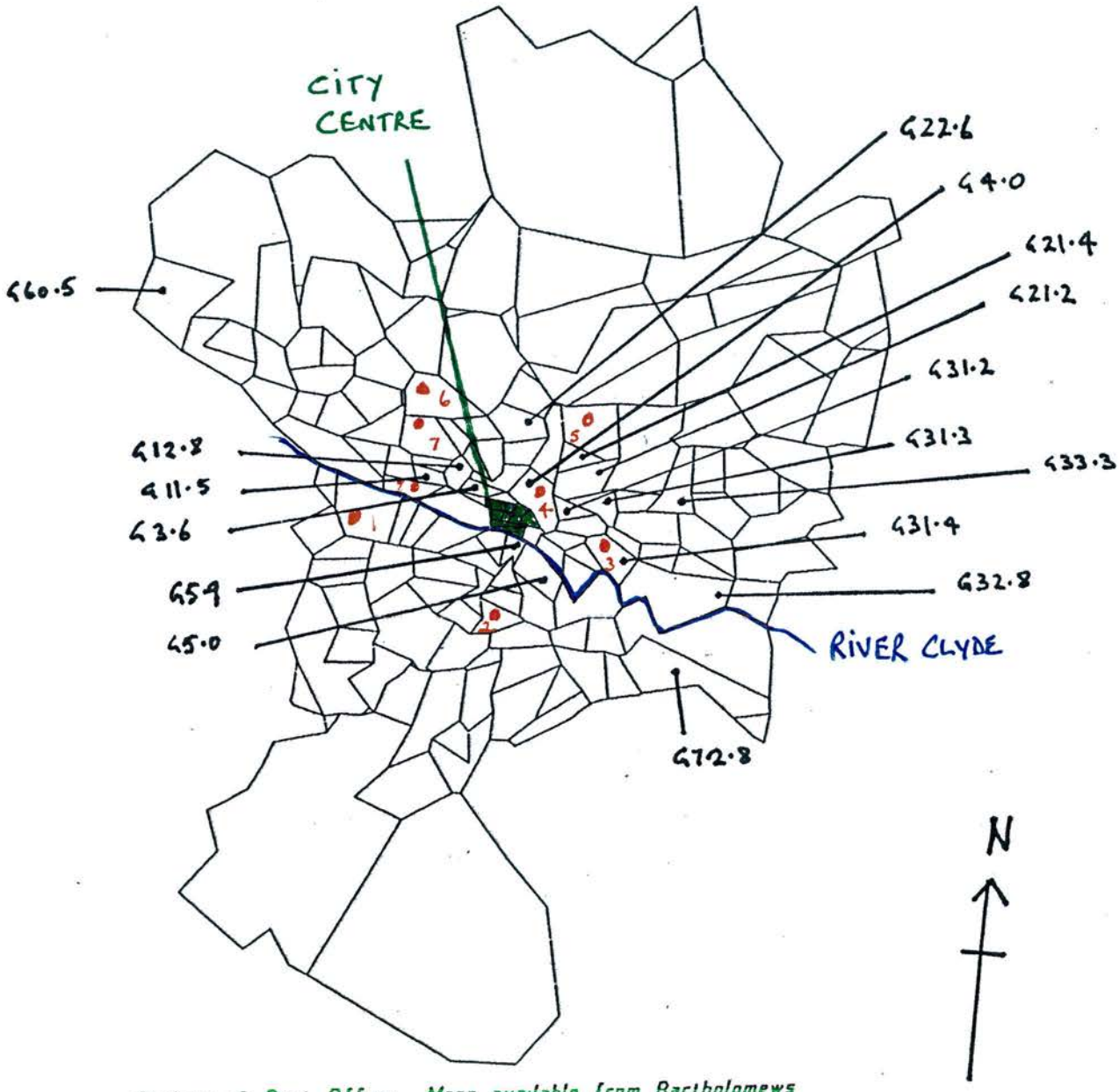
GGHB-key postcode sectors and other features



GGHB-key postcode sectors and other features



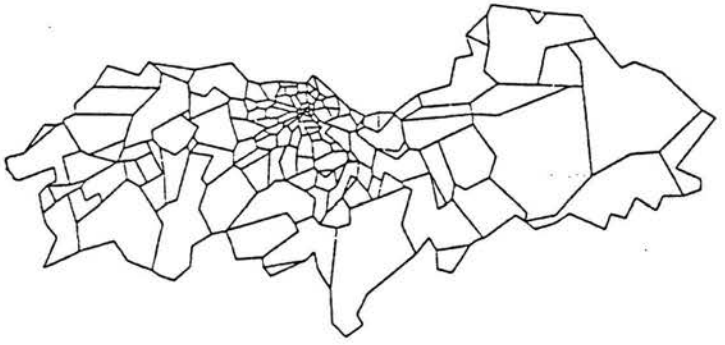
• = General hospital.

1 = Southern General 2 = Victoria Infirmary 3 = Belvidere

4 = Glasgow Royal Infirmary 5 = Stobhill

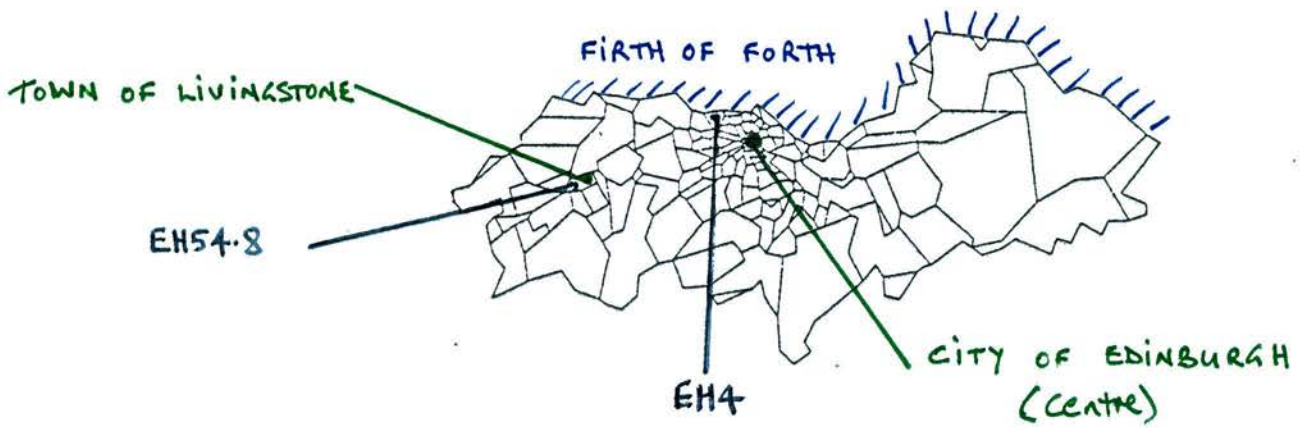
6 = Ruchill 7 = Gartnavel 8 = Western Infirmary.

Lothian Health Board-location of key postcode sectors and other features



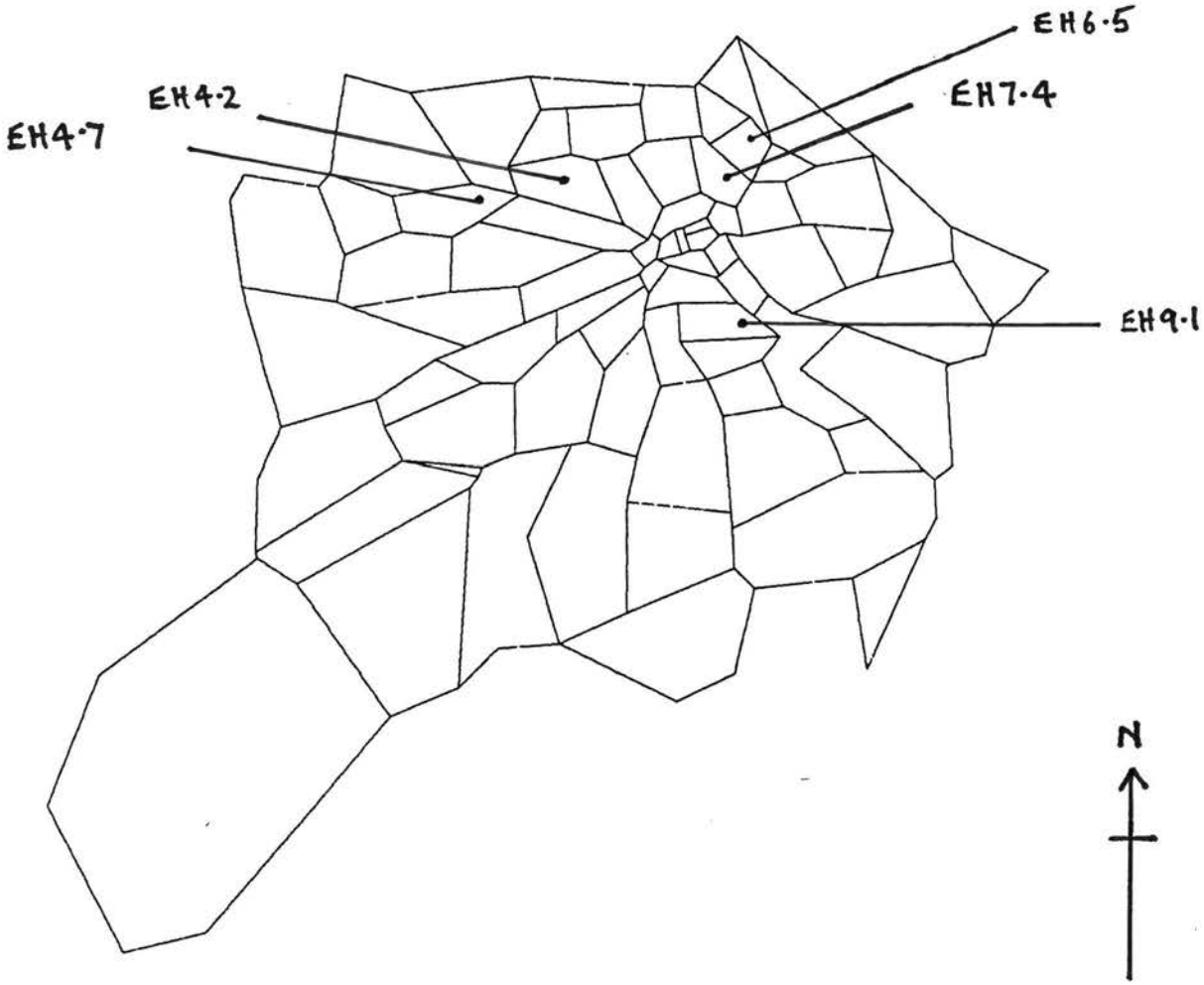
Subway © Post Office Maps available from Bartholomews

Lothian Health Board-location of key postcode sectors and other features

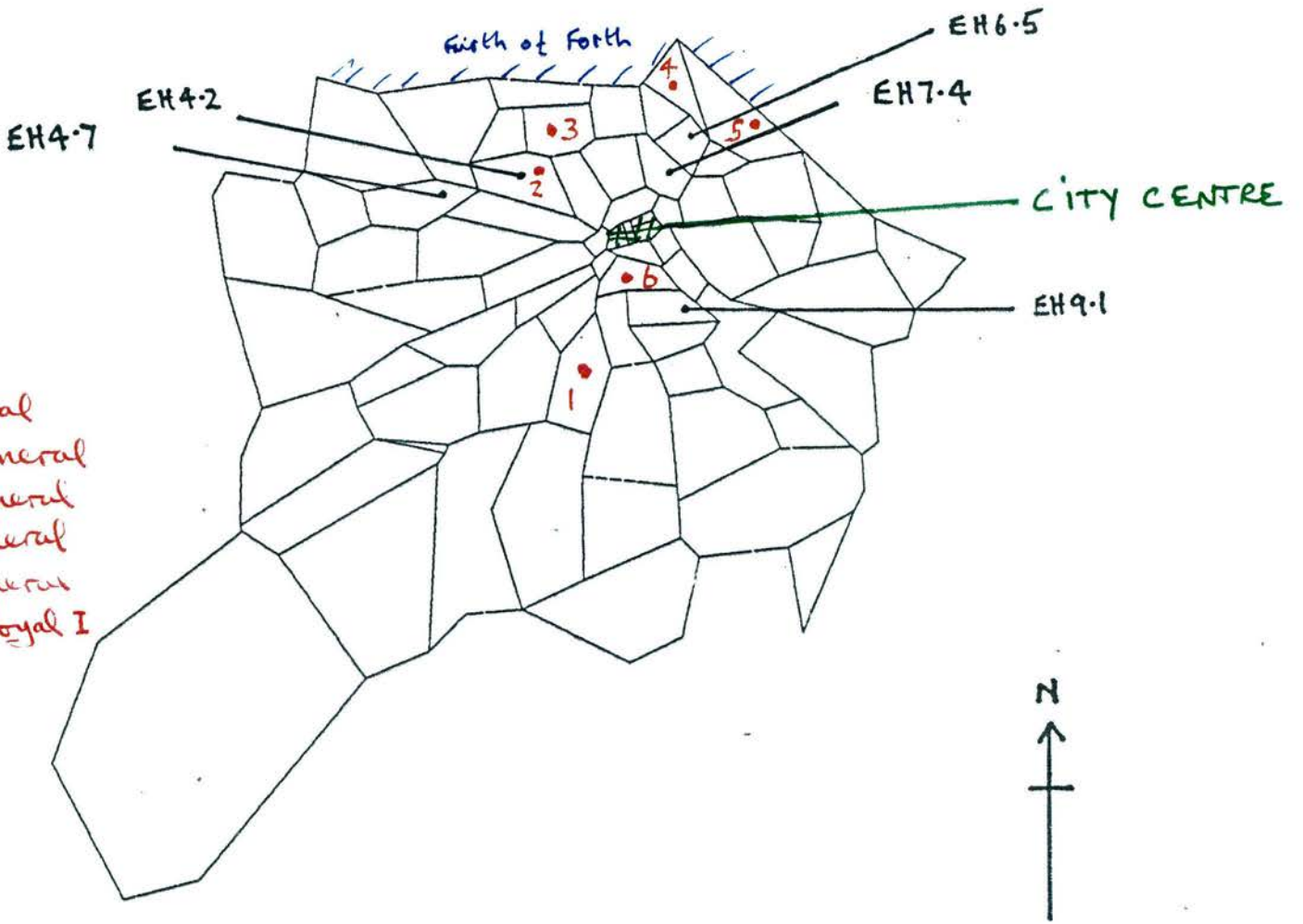


Subject to Post Office Maps available from Bartholomews

Edinburgh City-key postcode sectors and other features



Edinburgh City-key postcode sectors and other features



● = HOSPITAL

1. City Hospital
2. Western General
3. Northern General
4. Eastern General
5. Eastern General
6. Edinburgh Royal I